Exhibit F

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: *Wave 5 Cases*	

June 19, 2017

Expert Report of Shelby F. Thames, Ph.D.

I have been asked to analyze Ethicon's Prolene, the mesh material at issue in this medical device, and offer opinions concerning claims that the mesh used in Ethicon's product is not suitable for implantation. I have analyzed several other claims involving Ethicon's mesh devices used for the treatment of stress urinary incontinence and pelvic organ prolapse. Accordingly, I have included in this report my analyses of some of these products. I have also included in this report critiques of other expert reports offered in other cases in which Ethicon's mesh products have been at issue.

Ethicon's mesh product is made of Prolene mesh. Prolene is the Ethicon brand name for its mesh material. Chemically, Prolene consists of polypropylene plus the addition of five highly proprietary additives as discussed herein. Where I refer to polypropylene used in Ethicon's mesh, I am referring to the specific polypropylene and proprietary additives that make this mesh different from mesh marketed by other manufacturers. All my opinions herein are offered to a reasonable degree of scientific certainty.

I have been asked to do the following:

- Address the issues of Ethicon's Prolene as a material for use in the human body, its suitability for *in vivo* use considering its chemical and physical properties, propensity for degradation, material strength and viability, as well as longevity.

A copy of my Curriculum Vitae is attached as Appendix A. The materials I reviewed and/or relied upon in connection with the preparation of this report are listed in Appendix B. I am being compensated for my work in this matter at a rate of $400.00/hour.

In addition, I have directed the work performed by Kevin L. Ong, Ph.D., P.E. regarding cleaning, inspecting, testing and analyzing mesh explants, and I further rely upon the facts, opinions and data he has generated, which is incorporated herein. I also rely on my cleaning, inspecting, testing and analyzing mesh explants, as well as my prior testing, reports, and appendices prepared in this litigation.

Ethicon's mesh device made from Prolene is suitable for its intended use. Polypropylene (PP) has been used in medical devices for decades, and for good reason.[1,2,3] It is a polymeric species derived from the propylene monomer and is a durable, thermoplastic polymer composed exclusively of carbon and hydrogen. Polypropylene offers mechanical properties of durability and elasticity, it is the lightest major plastic with a density of 0.905 g/ml, and the crystalline character of isotactic polypropylene makes it the polymer of choice for properties of commercial interest.[4,5]

The monomer propylene (CH_2=CH-CH_3) shown in Figure 1, when polymerized, gives polypropylene; a polymeric species (many monomers) produced when many monomers are attached through carbon to carbon bonds, Figure 2.[6] The process of combining monomers together to form larger molecules is termed polymerization. Stated differently, a polypropylene polymer is a chain of propylene monomers linked together. Changes in process conditions and catalyst can lead to production of three configurations of polypropylene, and in the current instance isotactic polypropylene (iPP). The isotactic form of polypropylene possesses the configuration wherein the side-chain, or pendant –CH_3 (methyl) groups are aligned on the same loci of each tetrahedral carbon atom thereby forming an "iso" configuration (polypropylene) arrangement of each main-chain carbon atom shown in Figure 2.[7]

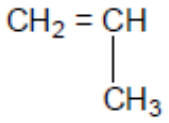


Figure 1. Propylene

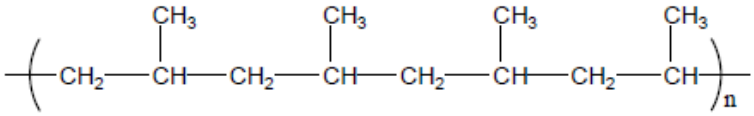


Figure 2. Isotactic form of polypropylene (iPP)

It is significant that PP consists only of carbon and hydrogen atoms. This organic composition of only carbon and hydrogen and its structure favors inertness, or in layman's terms, a material that is non-reactive to most environments. PP contains no polar groups such as sulfur, nitrogen, or oxygen. Such groups are different in electronegativity than carbon and thereby when

present, create a molecular environment of polarity.[8] However, with all main-chain carbon atoms of the same electronegativity, the PP molecule is homogeneous in electron density and thus is not polar. Therefore, there is no driving force for polar (species with negative or positive character) chemicals to be attracted to PP. An example of this concept is PP's high resistance to a common polar molecule, e.g. water (H_2O). Although it is very difficult to create a polymer unreactive in all environments, the choice of a hydrocarbon polymer like PP is as good as one can get for this application, and was the proper choice for Ethicon. The only supposedly truly inert material is gold, and even it is reactive to aqua-regia, a mixture of concentrated nitric and hydrochloric acids. I am unaware of any completely inert material.

The term "degradation" is commonly used to describe structural modifications from its pristine state.[9] However, I prefer "aging process" as molecular changes occur with time and use; such changes may be favorable or unfavorable. The process of molecular change is a function of use environment, chemical structure, and polymer composition. With respect to isotactic polypropylene (iPP), it is a chain of identical monomers linked or bonded together and, like other materials, it resists change but when change occurs, it is generally a function of environment and temperature. A structural change process seeks molecular site(s) most susceptible to change or alteration. For instance, if a hetero-molecular species such as an organic ester is used in an aqueous or water medium, a major concern would be hydrolysis wherein formation of an acid and alcohol would result. This change could be favorable should one desire to form an acid or alcohol, but unfavorable if ester stability was the intent. In the latter, it would be better to select a non-aqueous use environment or a different polymer type.

In general, the following are contributing factors to molecular changes:

(1) Light interactions

(2) Temperature-especially elevated temperatures

(3) pH

(4) Water

(5) Environment which may be a combination of 1-4.

From a molecular formula perspective, PP favors inertness because there is nothing in its polymer chain to: (1) attract water; or (2) that an acid or base would want to attack. It possesses no inherent polar groups, and not surprisingly, is water insoluble.[10] Furthermore, temperature exposure is minimal given body temperature (i.e. 37ºC). The pH or acid-base characteristics of the body are very modest.[11] Its use is in the body and, therefore, is not exposed to sunlight or external elements. PP is sensitive to sunlight, and can undergo significant changes in the exterior if not protected by ultraviolet inhibitors.[12]

It is not surprising, therefore, that the chemical composition of a polymer can introduce sensitivity to one or more of these factors. Although the degree of exposure to any of these is important, exposure to light and water in combination with temperature are, in my view, potentially the most likely to initiate and affect subsequent molecular changes.

UV LIGHT

In the present instance, the effect of light is not a factor because the mesh is not exposed to ultraviolet (UV) light *in vivo* and possesses more than sufficient physical properties such as strength, elasticity and toughness. The structure of Prolene and/or PP can be altered by exposure to ultraviolet radiation.[13]

TEMPERATURE

Likewise, temperature is not a factor of degradation for iPP *in vivo*. It is well known that high temperatures favor thermal degradation but, the thermal stability of iPP is well beyond that of the use environment (37ºC). Several properties of Ethicon's Prolene were confirmed by testing a pristine Ethicon TVT device No. 810041B which consists of the same Prolene material used in Ethicon's mesh products at issue in this litigation. Differential Scanning Calorimetry (DSC) confirmed Prolene's melting point of 162.6ºC or 325ºF (Figure 3). Its excellent thermal stability was established by thermo-gravimetric analysis (TGA), with weight loss beginning only at 333ºC or 631ºF (Figure 4). Consequently, *in vivo* thermal stability is clearly not a concern, and physical property determinations confirm the suitability and toughness of the Prolene fiber.

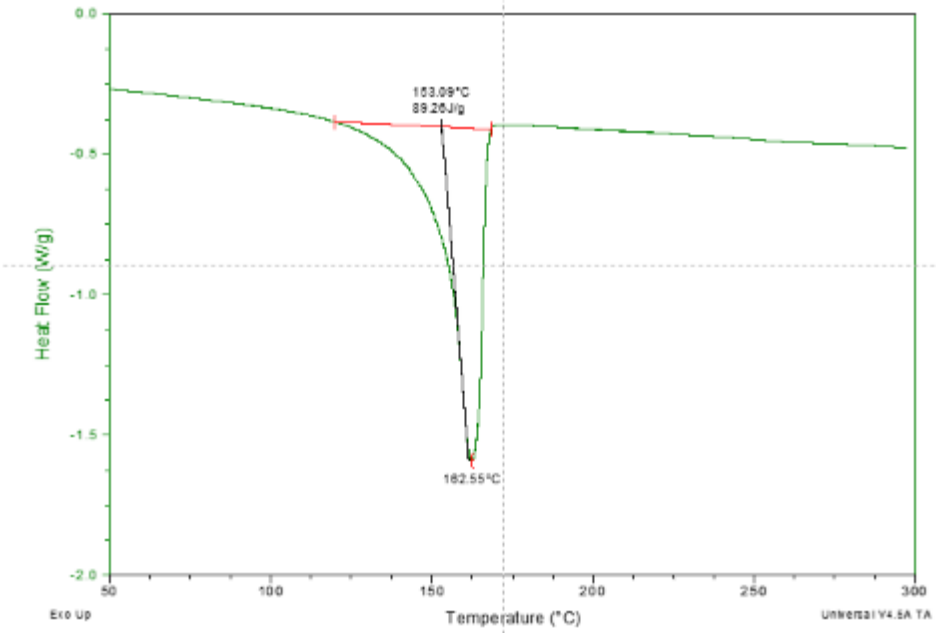


Figure 3. Differential Scanning Calorimetry (DSC) of pristine Ethicon TVT device No. 810041B – Lot 3694576

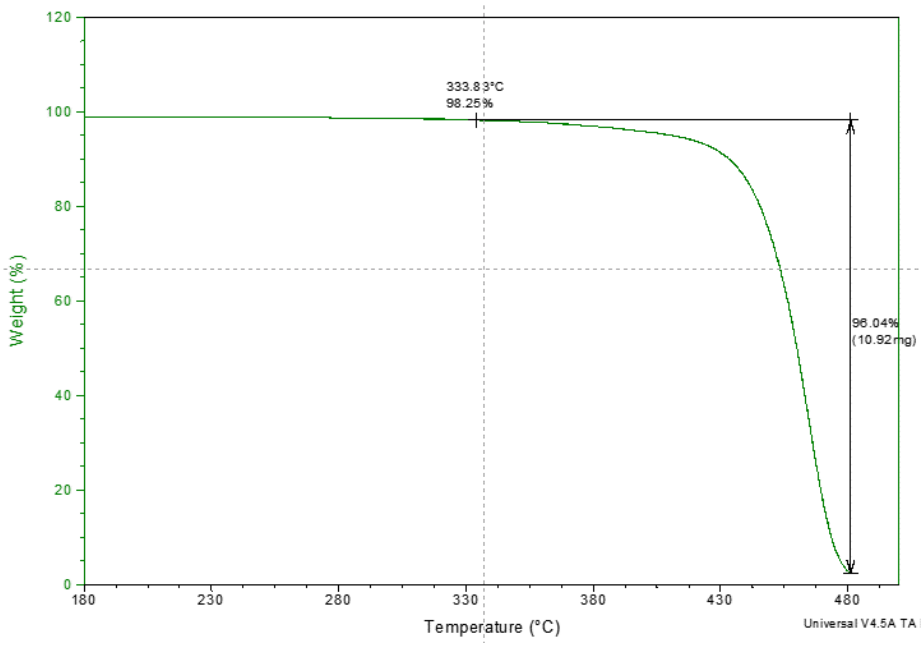


Figure 4. Thermogravimetric Analysis (TGA) of pristine Ethicon TVT device No. 810041B – Lot 3694576

pH:

The degree of acid or basic character is defined by pH. The scale of pH is from 1 to 14, with values less than 7 being considered acidic, and values above 7 basic. Seven is considered neutral on the pH scale. Highly acidic materials (less than pH 7) are materials such as sulfuric acid, nitric acid, hydrochloric acid, and to a lesser extent, acetic acid while basic materials (higher than pH 7) for example are lye and ammonia. The human body is neither highly acidic nor highly basic.[14] pH is a function of the hydrogen ion concentration (H^+) and since PP possesses no polar character such as H^+ it has no pH.

WATER RESISTANCE:

Prolene and PP are very water resistant, highly water insoluble, and polyolefins like PP are also highly impermeable to water vapor.[15] PP's resistance to water and water vapor, along with its other properties herein enumerated, make it an ideal polymer for *in vivo* applications. By way of example and noted earlier, it is well known that polyesters, as hetero chain polymers, are sensitive to hydrolysis whereby the carbonyl-ester linkage is split into an alcohol and the respective acid.[16] Should the ester functionality be a portion of the polymer backbone, polymer degradation by hydrolysis occurs; not so with PP given its continuous carbon-carbon, non-polar, and water resistant backbone skeleton. Williams further notes that "the activation energy for the degradation of high molecular weight polymers used in surgery vary from 30 kcal/mole to 80 or 90 kcal/mole, and such reactions generally require either heat, UV light or high energy radiation, preferably in the presence of oxygen, to proceed. It seems certain from these conditions that no such degradation should occur within the confines of the human body."[17]

In conclusion, I believe that Ethicon's Prolene material used in its mesh products does not undergo meaningful or harmful degradation *in vivo*. I am bolstered in my belief by a forward-looking seven year dog study conducted by Ethicon in November, 1985 and reported October 15, 1992, which confirm my personal investigations.

The Burkley dog study was undertaken to determine long-term stability of implanted Prolene sutures.[18] Daniel Burkley of Ethicon utilized FTIR spectroscopy to identify suture material, as more than one polymeric product was involved in the study. He reported IR spectra of Prolene and conservatively noted "possible evidence of slight oxidation" via "a broadened weak absorbance at about 1650 cm^{-1}." However, I believe this to be a mis-assignment because it is unclear how the explants were cleaned and processed, if at all. This absorption frequency is within the range of proteins which would be expected to be present on non-cleaned Prolene surfaces after years of implantation. He further performed gel permeation chromatography (GPC) to determine molecular weight (polymer size) of explanted and pristine Prolene suture controls. The seven year data confirmed no significant difference in molecular weights for the 4/0 Prolene control suture and the seven year explants. These are significant data and confirm Prolene's *in vivo* stability over the 7year period. The Prolene study continued with examinations via light microscopy, scanning electron microscopy, and physical property testing.

Burkley performed physical property determinations via measurements of tensile strength, elongation, and Young's modulus. These are extremely valuable data and very instructive in understanding the exceptional durability of Prolene during and after *in vivo* implantation. The elongation of explanted sutures increased 111% over the seven year period, tensile strength diminished by only 5%, and modulus decreased by 70%. The net result is a more durable, strong, elastic, tough, and pliable suture after 7 years implantation.

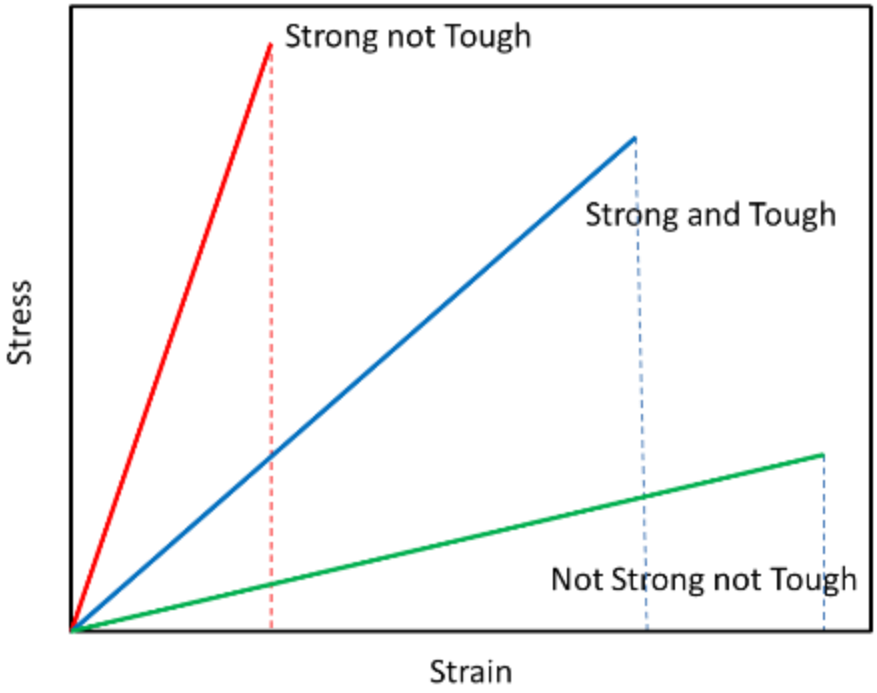


Figure 5. Stress-Strain Curve of Polymers Types

Figure 5 demonstrates the relationship between tensile strength (stress) and elongation (strain) for polymeric materials such as the Prolene mesh material in the product at issue in this litigation. The ultimate tensile strength is defined as the tensile strength at which a polymeric material (in this case Prolene) breaks and the ultimate elongation is the elongation at rupture.[19] In viewing Figure 5, it is evident that less elastic materials possess high strength and break at a relatively low percent elongation. These materials are strong, but not very elastic, and, therefore, not tough. Very elastic materials are those with high elongation requiring little stress to elongate the sample; these materials are not strong and not tough. However, materials requiring both high stress and elasticity before breaking are considered tough and durable (e.g. polypropylene). Toughness can be defined as the area under the stress-strain curve or as:[20,21]

> A measure of the ability of a material to absorb energy. The actual work per unit volume or unit mass of material that is required to rupture it. Toughness is proportional to the area under the load-elongation curve from the origin to the breaking point.[22]

Burkley reported load vs. elongation data in his 7 year dog study and as noted, toughness is proportional to the area under the load-elongation curve.[23] Since toughness is proportional to the area under the curve, these data prove that implantation over the 7 year period improved Prolene's physical properties and toughness improved. This is expected given plasticization can improve polymer toughness.[24] It is well known that plasticizers are used to reduce intermolecular interactions and facilitate molecular mobility and, in doing so, can reduce tensile strength with a corresponding increase in elongation.[25,26,27] The plasticization/toughening effect is precisely what is manifested in the 7 year dog study and demonstrated in Figure 6.

Clearly, given toughness was improved after initial implantation, as noted in (Figure 6), there is absolutely no suggestion of, or support for, Environmental Stress Cracking (ESC) as a destructive mechanism during implantation or any other evidence of degradation. Moreover, it is reported that PP is "completely free from environmental stress cracking."[28] Others attempting to establish conditions for ESC of PP have not been successful.[29]

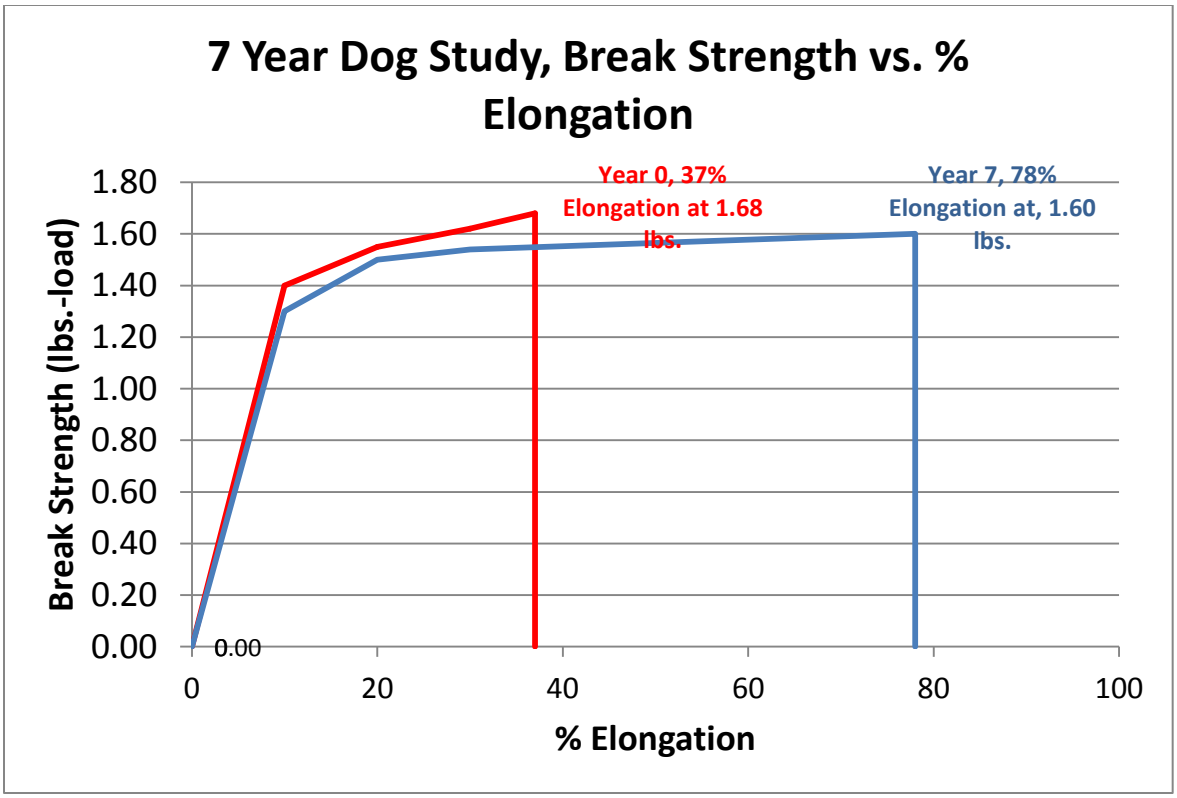


Figure 6. Plot of Burkley 7 Year Dog Study Data

In further support of *in vivo* stability of Prolene, Burkley performed molecular weight determinations by Gel Permeation Chromatography (GPC) and found no meaningful change over the 7 years of implantation. These data are exceedingly important, instructive, and consistent with the physical property (toughness) data already noted. For instance, it is well known that molecular weight reductions adversely affect physical properties.[30] Gahleitner and Fiebig discuss physical and chemical changes in materials as a function of molecular weight in the following statement, "In contrast to other polyolefins, such as PE or most olefin-elastomers (EPR, ethylene-propylene-diene rubber (EPDM), radical reactions in PP cause mainly a degradation effect, reducing the average chain length of the polymer and especially affecting the high molecular weight fraction. As these are of primary importance for the mechanics of the system-through their activity as inherent nucleants as well as their function as 'tie molecules' between different crystalline sections-a significant reduction of mechanical properties can also be expected. The normal consequence is embrittlement, a massive decrease in toughness."[31]

Taken in totality, Burkley's physical property/toughness data validates toughness "improvement" after the initial implantation, and confirms no meaningful loss in molecular weight. Had there been a significant change in molecular weight after implantation, Burkley would have found a massive decrease in toughness of the explanted sutures, as well as suture embrittlement as taught by Gahleitner and Fiebig.[32]

Burkley's study is further supported by the work of plaintiffs' expert[33] who performed molecular weight determinations of explants for more than 15 patients with no significant molecular weight

changes. The plaintiff's expert molecular weight data was consistent with Burkley who performed six GPC molecular weight determinations on dogs with no meaningful molecular weight changes.

These data are consistent with no meaningful molecular weight changes having occurred during 7 years implantation. George Wypych reported that "Molecular weight of PP decreases on exposure to UV radiation due to the chain scissions in surface layers."[34] Had Burkley or plaintiff's expert found any significant molecular weight loss, tensile strength, elongation, and toughness properties would have declined precipitously.

These authors also report "Tensile strength and strain values change linearly with carbonyl index concentration," or simply the accumulation of carbonyl groups with exposure or use time.[35] Carbonyl groups are well known to be a primary product of PP degradation. If carbonyl groups develop during use, molecular weight losses of PP will occur. It is, therefore, obvious that molecular weight and carbonyl group formation or appearance are inextricably linked and you cannot have one without the other, as noted in Figure 7.

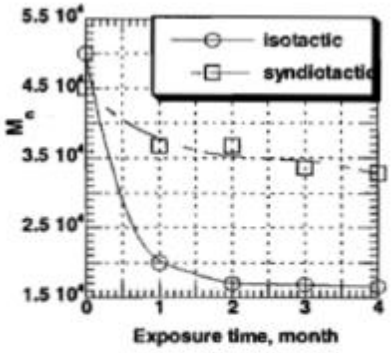


Figure 14.107. Number average molecular weight of iso- and syndiotactic polypropylenes vs. irradiation time with mercury lamp through Pyrex filter. [Data from Kato, M; Tsuruta, A; Kuroda, S; Osawa, Z, *Polym. Deg. Stab.*, 67, No.1, 2000, 1-5.]

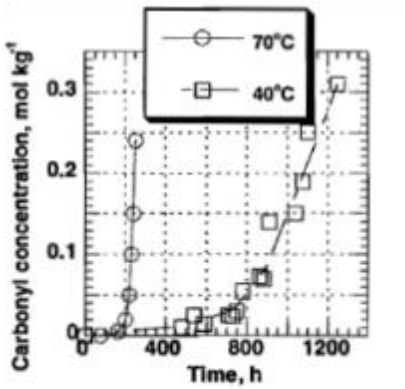


Figure 14.108. Effect of temperature on carbonyl group concentration in polypropylene exposed to fluorescent lamp radiation in the range of 300-500 nm. [Data from Audouin, L; Girois, S; Achimsky, L; Verdu, J, *Polym. Deg. Stab.*, 60, 1, 137-43, 1998.]

Figure 7. Relationship between molecular weight and carbonyl group formation in polypropylene.[36]

Burkley's 7 year dog study findings are consistent with the following data in that;

- Prolene's molecular weight did not change significantly over the 7 years of implantation;
- No carbonyl absorption frequencies were sufficient to determine a carbonyl index concentration;
- Physical properties of the Prolene explant did not deteriorate but, instead, improved during implantation; and
- Prolene is stable *in vivo*

Had Prolene degradation occurred, there would have been significant losses in toughness, molecular weight, and a concomitant appearance and increase in carbonyl frequency; none of which occurred during the 7 year dog study.

In summary, plaintiff experts' arguments for degradation, oxidation, and molecular weight losses after initial implantation are not supported by Burkley's data. Instead, the results of Burkley's 7 year dog study is proof positive that Prolene is absolutely stable *in vivo*. Furthermore, plaintiffs' experts' data, and published literature developed from reliable scientific data also supports Prolene's *in vivo* stability

I understand there are those who allege Prolene's structural changes *in vivo* are sufficient to affect property/device function loss. However, this tenet is not founded on factual, reliable and repeatable scientific data of which I am aware. It is my opinion, supported by extensive and repeatable experimental data, that such proponents have historically, and erroneously, identified adsorbed protein coatings on the implant surface as polypropylene; they are mistaken. The adsorbed protein coating forms *in vivo*, and is subsequently "fixed" by the well-known chemical reaction of formaldehyde with proteins.[37,38] The fixation product has not been removed, in the instances of which I am familiar, prior to explant testing and evaluation. Thus, these proponents have mischaracterized adsorbed protein coatings as PP and, to date, the scientific and chemical basis of their argument is non-existent.

The work of de Tayrac and Letouzey, who did not use formaldehyde as a fixation agent, further confirms this precept. De Tayrac writes that "The explanted infected mesh shows transverse cracks (a). After washing with DMSO (b) and ultrasonic shock (c), it appears marked modifications in mesh surface corresponding to the biofilm (a), and after biofilm removal, no polymer degradation was seen any more(c)." (a, b, and c are photos of explanted PP at the various stages of cleaning). Note, contrary to others who report Prolene degradation, de Tayrac did not "fix" the proteins of his sample via immersion in formalin (formaldehyde in water) solution. This is extremely significant as the fixation process produces a hard, insoluble, and brittle protein-formaldehyde polymer composite shell surrounding the fiber. It is significant that de Tayrac's decision not to use formalin fixation as part of his experimental protocol allowed him to examine the fiber without interference of the encapsulating protein-formaldehyde polymeric composite. Consequently, he was able to clean the fibers with mild reagents and conditions. In summary, when properly handled and cleaned without "fiber fixation," the fibers were devoid of a protein coating layer and essentially unchanged.

Much has been written, and literally thousands of experiments conducted, in an effort to ascertain the interrelation of synthetic mesh materials, their function, and performance in the human body. In studying these issues, I have confirmed an alarming and almost universal indifference for the underlying basic chemistry/biochemistry necessary for evaluating the efficacy of mesh materials. For instance, the typical protocol for removing mesh has been to perform explant surgery, and thereafter subject the explanted material to a variety of analytical procedures. The procedures used by pathologists are instructive in establishing an explant's appearance, and properties, as noted by a variety of microscopy evaluations. A typical sequence of process steps is shown below.

The Explant Process Steps:

1. Surgeon removes explant.

2. Surgeon immediately places the flesh imbedded mesh explant in a preservative, i.e. typically a 10% formalin solution whereupon the formaldehyde-protein "fixation chemical reaction" begins immediately. Proteins necessary for this reaction are derived from human flesh and fluids (collagen).

3. The formaldehyde reaction with protein(s) produces a crosslinked polymer that forms a shell around and adhered to the explanted mesh fibers. The newly formed polymeric shell is hard, brittle and insoluble.[39]

4. The same hard, brittle and insoluble formaldehyde-protein polymer composite encasing the Prolene fibers from Steps 2-3 must be removed if the fibers are to be properly analyzed. If the formaldehyde-protein polymer is not removed from the mesh fiber, any subsequent spectroscopic and chemical analyses are highly suspect and almost assuredly are in error. If a cleaning process is not performed, or is unsuccessful, the residual formaldehyde-protein polymer will interfere with subsequent testing and, therefore, make accurate and scientifically valid data interpretation difficult if not impossible.

5. Typical analyses to which I refer include: Fourier Transform Infrared spectroscopy (FTIR), light microscopy (LM), scanning electron microscopy/energy dispersive x-ray analysis (SEM/EDS), differential scanning calorimetry (DSC), thermos-gravimetric analysis (TGA), and mechanical property evaluation (toughness via tensile strength, elongation, modulus).

6. Available scientific data is collected from the conducted analyses, and expert opinions are formed and presented.

This generalized process was followed by a number of investigators cited in these matters, including Drs. Iakovlev,[40,41,42,43] Celine Mary, Clavé, Liebert, Costello, Ostergard, Rosenzweig, Klinge, etc. However, none properly considered the presence of the hard, brittle and insoluble shell of the protein-formaldehyde polymer surrounding the explanted mesh and its consequences. This well-known basic chemical reaction was missed by these investigators, authors, and apparently many others. As a result, significant amounts of unreliable and confusing data now permeate the media with regard to mesh explants and their propensity for surface cracking. For example, consider the manuscripts/opinions of some who have missed the consequences of this basic chemistry:

CLAVÉ

Clavé's investigation included a "sample of 100 implants explanted from patients, due to complications, was examined to evaluate the relative degradation characteristics of polypropylene (PP) and polyethylene-terephthalate (PET) prosthetics."[44] Clavé's explants, all 100, were "fixed" with formalin, and he used NaOCl exclusively with a deionized water rinse for cleaning. Our work has shown this cleaning protocol is insufficient for complete removal of

"fixed" protein-formaldehyde polymers.[45,46] Clavé makes no mention of the "fixation product", and likewise does not speak to or confirm its removal prior to a series of analyses; he notes only that the "FTIR absorption bands between 1616 and 1650 cm^{-1} could be attributed either to carboxylate carbonyl or to residual products of biological origin. Therefore, these results cannot confirm the formation of carboxyl groups *in vivo*." He further disregards the absorptions in the 1600 cm^{-1} region as they are indeed of biological origin in that they are characteristic absorption frequencies for proteins. Meaning, of course, that the samples he evaluated were not completely cleaned and free of the adsorbed protein layer on the fiber surface. While the frequencies in the 1600 cm^{-1} region are diminished after cleaning, they are not absent in totality. He further writes that "The absorption band at 1730 cm^{-1} could correspond to the absorption of ester carbonyl groups, which is likely from esterified fatty acids. However, some samples of group 2 also showed that the absorption band at 1730 cm-^{1}, and they were not deemed damaged." That is absolutely what one would expect as fatty acids would not, and cannot, damage Prolene or PP as proven by Burkley's dog study. Instead they serve as a plasticizer, and improve polymer physical properties.[47] Clavé continues by writing that "Additionally, FTIR analysis did not conclusively confirm that the degradation was due to oxidation" and "None of these (hypotheses), particularly direct oxidation, could be confirmed in this study."[48] Thus, Clavé studied 100 explants and readily admits that in none of the 100 explants could he find damage due to oxidation; thus, PP was not oxidized in any of the 100 explants given his results and his conclusions. Yet, his work is frequently cited as showing that PP degrades *in vivo*. This is an example of one individual's unfounded opinion being referenced by another, and the myth propagates over and over again.

LIEBERT

Liebert and co-workers investigated extruded filaments of unmodified PP with and without antioxidants in order to determine their rate of degradation.[49] For his experiments, Liebert purchased polypropylene pellets from Hercules and extruded it in his laboratory. Some extruded polypropylene contained antioxidants and some did not. For his antioxidant-containing sample, he used the antioxidants prescribed by an FDA approved proprietary stabilizer system. He begins his dialogue by writing that "No change in the infrared spectra or tan delta (T_g) was observed, however, for implants containing an antioxidant." He goes on to note that "Thus, it is apparent that polypropylene filaments implanted subcutaneously in hamsters degrade by an oxidation process which is retarded effectively by using an antioxidant."

Yet, even given Liebert's own admission for lack of evidence of oxidation, there are those who cite his work as proof that Ethicon's Prolene oxidizes *in vivo* (see Celine Mary).[50] It is well known and uncontested that polypropylene formulated without antioxidants are subject to oxidative degradation; however, is it equally well known that Ethicon properly protects its Prolene mesh products with a combination of two highly effective antioxidants. At the time of this writing, I have seen no scientifically sound evidence to prove Ethicon's Prolene mesh oxidizes *in vivo*.

MARY

This investigation was conducted by a number of supporting individuals, one of which was Dr. Robert Guidoin. The article focuses on evaluating polyvinylidene fluoride (PVDF) as a substitute for Prolene.[51] The investigation utilized Prolene and PVDF sutures implanted in dogs,

explanted, and "cleaned." The explants were either fixed in glutaraldehyde and post fixed with osmium tetroxide or fixed in a 10% solution of formalin. However, no data was provided to confirm complete cleaning or removal of the aldehyde-protein polymer that inextricably forms about the Prolene fibers. Furthermore, the authors state "After cleaning to remove adhering tissue, their relative biostability was assessed in terms of surface morphology and chemistry using scanning electron microscopy and Fourier transform infrared spectroscopy." However, no scientific evidence was presented to confirm complete cleaning, although the authors used surface morphology studies to establish their relative biostability claims. In fact, the authors state, "The surface of the cleaned and control sutures were inspected in the scanning electron microscope to assess any surface modifications." Furthermore, note that only one FTIR frequency, 1740 cm^{-1}, an absorption frequency of DLTDP, an ingredient of Prolene's formulation, was reported in this manuscript. However, Mary was unaware that formulated Prolene contained DLTDP, a carbonyl containing chemical, given her statement, "both pure polymers are devoid of this functional group (meaning a carbonyl group)." While she is correct that both "pure" polymers are devoid of this functional group, she is totally unaware that formulated Prolene possesses the carbonyl frequency by presence of its component, DLTDP. Consequently, her entire paper is meaningless and bears no significance. Moreover, by not having benefit of the entire FTIR spectrum, scientists reading this manuscript cannot determine if other important FTIR frequencies are present, such as lipid esters, carboxylic acids, and proteins; all of which possess carbonyl frequencies. Such reported data, and lack of other essential data, is confusing and brings lack of clarity to this manuscript. For instance, Celine Mary and her colleagues cite the work of Liebert as "identifying" an oxidation process, chain scission, and the formation of carbonyl groups…, yet Celine Mary and colleagues fail to include a very critical fact that Liebert did not exclusively use antioxidant stabilized PP samples. Liebert clearly states in his conclusion statement that, "Infrared Spectra and mechanical testing of implanted and non-implanted filaments containing an antioxidant show no changes in chemical or physical properties as a result of implantation."[52]

COSTELLO

First and foremost, the mesh materials were procured, "fixed" in formaldehyde and "cleaned" according to the following process:

"After explanting, meshes were immersed in a 10% v/v formalin solution and stored at room temperature. Prior to testing, any adherent tissue was removed from the meshes by soaking in a sodium hypochlorite solution for 2 h at 37ºC (6–14% active chlorine, Sigma Aldrich, St. Louis, MO). Each mesh was then rinsed several times with distilled water to remove any residual sodium hypochlorite solution and allowed to dry overnight."[53]

It is exceedingly important to note that Costello failed to perform FTIR analyses for chemical identification, or any other tests, to confirm complete cleaning of the protein coating residue and its removal from the explants. Thus, that he relied on the hypothesis the explants fixed in formaldehyde were completely cleaned, without any scientific evidence to affirm his tenet, does not allow serious consideration of its contents by the scientific community. Moreover, our work clearly and definitively confirms the fallacy of his conclusions.

His statement, “the results from SEM, DSC, TGA, and compliance testing provided strong support that oxidative degradation was occurring *in vivo*” cannot be taken seriously given his lack of understanding of the formaldehyde-protein encased fiber.

The Costello DSC results are also suspect given no consideration to the presence of residual lipids (fatty acids), which are plasticizers and will lower the melting point.[54,55,56]

Costello, in his discussion section, makes the following statements; “The SEM micrographs displayed images of materials that were vastly different in topology than the pristine materials. The micrographs of explanted polypropylene materials exhibited cracks, surface roughness, and peeling indicative of surface degradation while the pristine materials appeared smooth.”[57] Once again, conclusions are drawn with regard to SEM micrographs of PP without any regard for the protein-formaldehyde composite formation or any scientific evidence of a truly cleaned Prolene or PP surface.

Furthermore, he admittedly makes an unfair comparison between heavyweight and lightweight PP in that the lightweight PP was implanted for 5 months and its heavyweight counterpart for more than 5 years. Costello states “However, micrographs of both heavyweight polypropylene components of the explanted composite mesh (Bard product) revealed micro-cracks in the transverse directions, as well as peeling of the top layer of the fibers.”[58] However, he provides absolutely no scientific data to confirm the “micro-cracks” are of Prolene or PP origin. One simply cannot look at a specimen under a microscope and determine its chemical composition.

Costello, like other authors, elected to investigate the possible oxidation *in vivo* yet he completely missed the presence of the formaldehyde-protein shell surrounding the explant fibers, and its importance.

OSTERGARD

In his “Current Commentary” writings published in the 2010 Obstetrics and Gynecology Journal, Ostergard states that “non-inert polypropylene degrades into potentially toxic compounds that would be expected to stimulate a greater inflammatory reaction leading to erosion.”[59] He does so based solely on the Costello 2007 SEM photomicrography in Surgical Innovation.[60] He further pens a “Clinical Opinion” in the International Urogynecological Journal (2011) and cites the work of Clavé.[61,62] Ostergard presents absolutely no original scientific data to support his tenet, but only references work of others to which I have already addressed.

The Process Steps. The Process Steps described herein rely upon each individual process being conducted efficiently and effectively with appropriate chemical/biochemical consideration given each step. It is to this issue, and particularly process steps 2-4, that I raise serious concerns.

Reasons for concern and the supporting science follow:

Protein adsorption on implant device surfaces

It is well established that implantation of a foreign body (mesh materials, as an example) elicits a foreign body reaction involving the immediate formation of tenaciously adsorbed and thus adhered "protein coating(s)" onto the surface of implanted material(s).[63,64,65,66] Kyriakides makes it very clear (Chapter 5 entitled Molecular Events at Tissue-Biomaterial Interface in the book *Host Response to Biomaterials*) that "Within seconds of implantation, proteins interact with the biomaterial surface and over time create a proteinaceous coating".[67] Kyriakides also states that body proteins adsorb onto implanted material surfaces and contact the surface even before cells reach the implant.[68] As a result, adsorbed proteins form a coating that encapsulates the biomaterial (implant) surface before cells arrive and begin their proliferation.[69] Consequently, cells do not come in contact with the foreign object but rather with an adsorbed and adhered protein surface.

Prolene is a material to which proteins will adsorb and readily adhere.[70,71] Schmidt and co-workers state "Within milliseconds after biomaterials come in contact with a biological fluid such as blood, proteins begin to adhere to the surface through a process known as protein adsorption." They further state, "By the time cells arrive, the foreign body material surface has been coated in a monolayer of proteins; hence, host cells do not "see" the material but "see" instead a dynamic layer of proteins.[72] Consequently, once cells finally arrive at the surface they no longer "see" the biomaterial surface itself but instead "see" a dynamic coating of adsorbed proteins." It is well understood and accepted proteins must first be adsorbed onto Prolene's surface, and thereafter "cells interact with surface proteins through direct binding to receptors on the cell membrane, but do not have receptors for a material surface alone without first contacting a coating of proteins."[73] Thus, there is no question that proteins (collagen) adsorbs onto Prolene and subsequently body cells flourish on the adsorbed proteins, resulting in encasement of the implant by a protein layer or coating. All proteins possess carbonyl groups characterized by the following chemical composition, i.e. –CONHR– or $–CONH_2$. Given these well-known precepts and an understanding of basic organic chemistry it is completely illogical for anyone to question or dispute the presence of an adsorbed-adhered protein layer on explanted Prolene surfaces. Therefore, it is equally imperative that the proteinaceous coating layer be removed from mesh material before testing mesh fibers; otherwise, an impure and uncleaned product is being tested and any test results are unreliable. For instance, if proteins are not removed, and their presence is not known and understood, they elicit erroneous data. Consider, for example, microscopy evaluations such as scanning electron microscopy (SEM) and optical microscopy (LM). If all tissue and proteinaceous coatings (i.e. adsorbed protein) are not removed prior to fixation or immersion in formaldehyde, a high molecular weight, brittle, and insoluble, protein-formaldehyde polymer forms. The formaldehyde-protein polymer encapsulates or, in other terms, forms a shell of "armor" around mesh fibers. During this chemical "fixation" reaction, molecular contraction or shrinkage occurs. Subsequent drying of the mesh explant produces a hard, brittle protein-formaldehyde polymer encasing the Prolene fiber. This dry and hard protein coating will crack as it surrounds the explant and experiences movement.[74,75] Examples of this phenomenon have been observed during my SEM examinations of explanted devices similar to the example depicted in Figure 8 below. It is from a plaintiff's expert in mesh litigation.

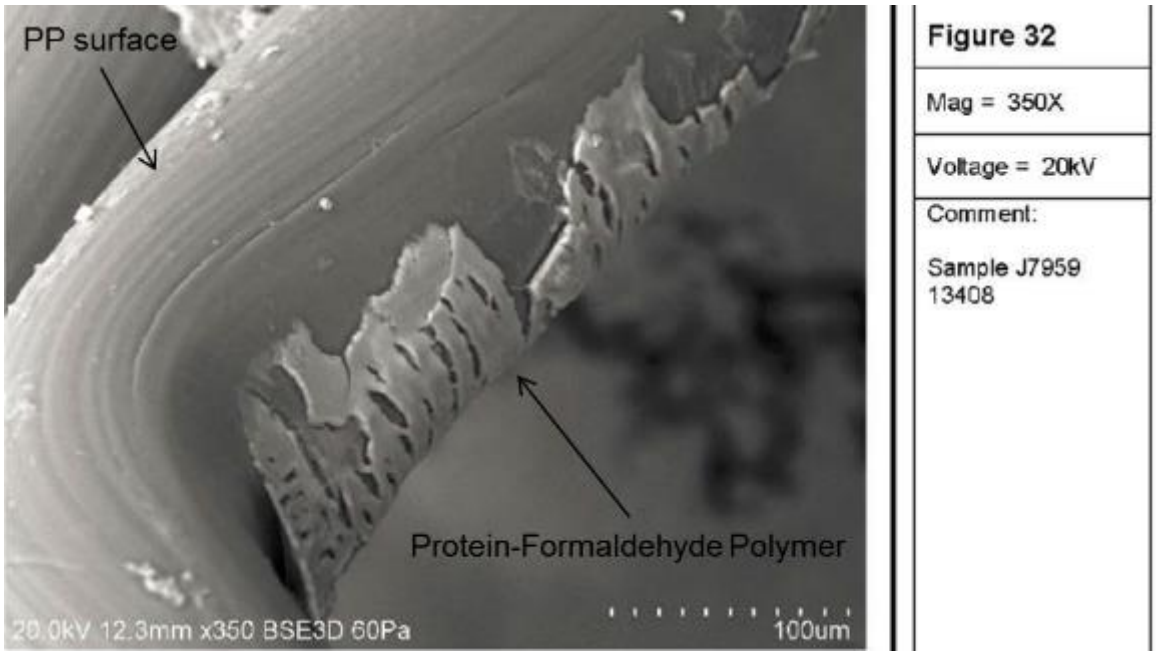


Figure 8. Example SEM micrograph taken from plaintiff's expert report in other litigation, confirming a cracked, encasing layer of protein-formaldehyde polymer.[76]

It is important to note that the surface striations or extrusion lines created during the extruding process of manufacturing Prolene fiber remain visible and unaffected after the protein coating begins to crack and fall from the fiber's surface. If surface degradation of Prolene actually occurred, the extrusion lines would no longer be present and surface pitting of Prolene would be evident; neither has occurred.

The chemical reaction of proteins with formaldehyde is well-known, and has been for more than 60 years. The reaction of formalin with proteins was made public in 1949 when the chemistry was first published by Heinz Fraenkel-Conrat and Dale K. Mecham.[77] It is also well established that adsorbed protein removal from a foreign body is very difficult.[78] These authors, one of whom is Dr. Robert Guidoin, wrote "In order to study the surface chemistry of explanted prostheses, it is necessary to remove all the tissue that may have grown over and within the prosthetic structure. In the event that the explant has been treated with a fixative agent after retrieval, such as formaldehyde or glutaraldehyde, the tissue will be crosslinked and the only effective way of completely removing it is to use hydrolytic chemicals. Depending on the degree of crosslinking, strong chemicals and/or extreme hydrolysis conditions may be required."

Fraenkel-Conrat in their 1949 publication clearly described the chemical reaction transforming protein with formaldehyde into a high molecular weight, crosslinked, formaldehyde-protein polymer. The chemical reaction is shown in Figure 9.

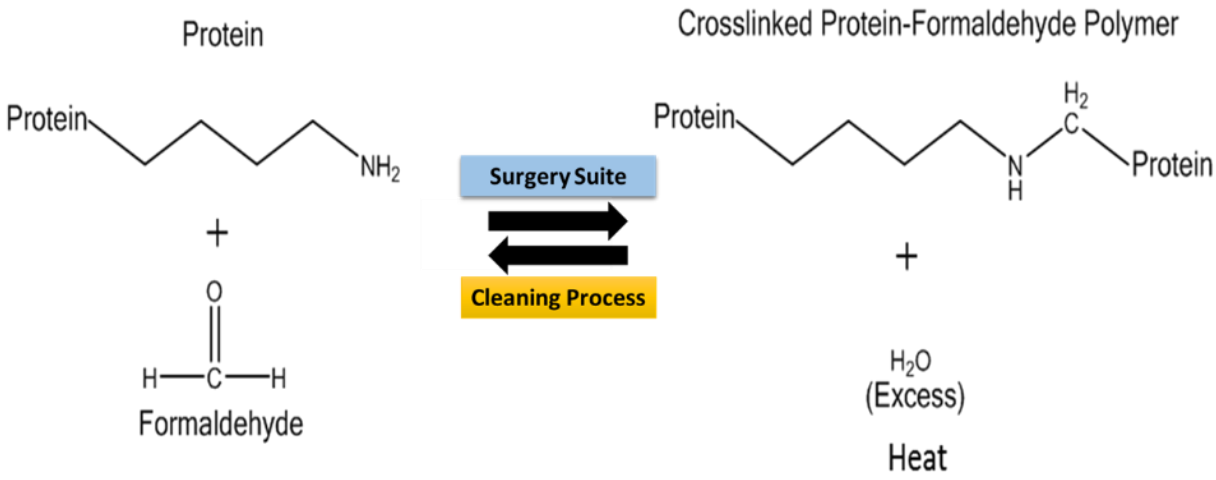


Figure 9. Reaction of protein and formaldehyde resulting in a crosslinked protein-formaldehyde polymer.

This chemical reaction, and its reversibility, is the basis for the cleaning protocol (see Figure 33) I developed and use to clean explanted mesh samples.

The formaldehyde-protein polymer properties are characterized by:[79,80]

- Insolubility
- Brittleness
- Hardness
- Contains at minimum, Carbon, Hydrogen, Oxygen, Nitrogen

The authors' 1949 manuscript stated "Preceding papers from this Laboratory have shown that at room temperature, and within the range of pH 3 to 9, methylene crosslinks can be formed between amino groups on the one hand and amide, guanidyl, indole, phenol, or imidazole groups on the other."[81] Numerous papers have since been written reaffirming what is a very well-known protein-formaldehyde crosslinking reaction.[82,83,84] In fact, Dr. Susan Lester has prepared a Manual of Surgical Pathology, 3rd Edition, copyrighted in 2000, 2006, and 2010 describing the fixation process.[85]

In support of Fraenkel-Conrat, *et al.*, Fox and co-workers wrote in the 1985 Journal of Histochemistry and Cytochemistry, and described formaldehyde as a tissue fixation chemical.[86] These authors brought attention to the work of Ferdinand Blum who, as early as the 1980's, was responsible for several articles on the reactions of formaldehyde as a "tissue fixation" agent. Fox, *et al.* reported when tissue is placed in formalin, "A major concern in fixation by formaldehyde, or with any fixative, is the amount of distortion produced by the fixation process. The usual term applied to fixation distortion is shrinkage."[87] These authors also note "A variety of concentrations of formaldehyde were tested for use as a fixative for electron microscopy, but

no concentration of formaldehyde between 0.5 and 20% produced photomicrographs comparable with those from glutaraldehyde fixed tissues."[88]

Lester, likewise, has written that "most fixatives cause shrinkage of the tissue and offers additional information regarding formalin as a fixative."[89] Dr. Lester in the text titled "Manual of Surgical Pathology"[90] writes:

1. If exact measurements are important, they should be taken prior to fixation.

2. Unbuffered formalin degrades rapidly. Composition: 10% phosphate-buffered formalin (formalin is 40% formaldehyde) in water, does not preserve nucleic acids well.

3. Formalin is the standard fixative of most pathology departments and has been used in many studies of special stains and immunohistochemistry. It fixes most tissues well and is compatible with most histologic stains.

4. Tissue can be preserved in formalin for many months. Fixation occurs due to crosslinking of proteins.

5. Crosslinking occurs over time; therefore, even small specimens (e.g., core needle biopsies) need to "fix" for a minimum of 6 to 8 hours

6. Formaldehyde, a highly reactive chemical and polar reagent, can function as an extraction solvent and/or chemically react with other non-protein chemicals, i.e. "Lipids and carbohydrates are often lost during processing unless special techniques are used."

In the review *Crosslinking fixatives: what they are, what they do, and why we use them,* the authors discuss formaldehyde and its preference for reacting with proteins during the fixation process.[91] These concepts are illustrated in Figure 10.

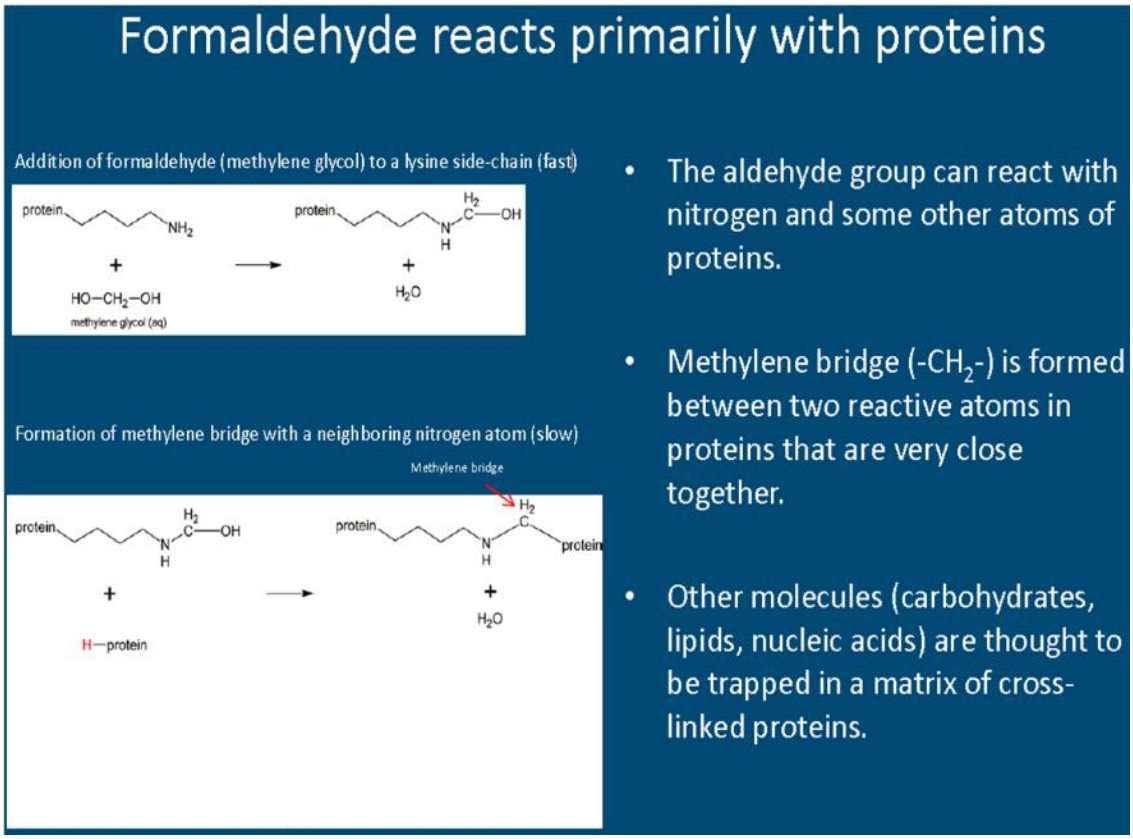
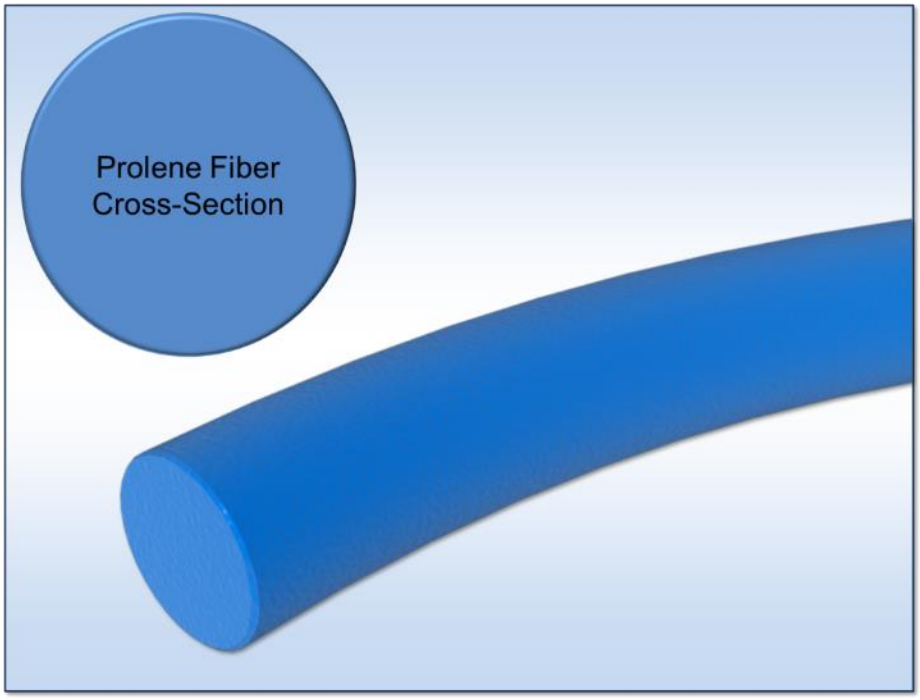


Figure 10. Formaldehyde reactions with proteins during the fixation process.[92]

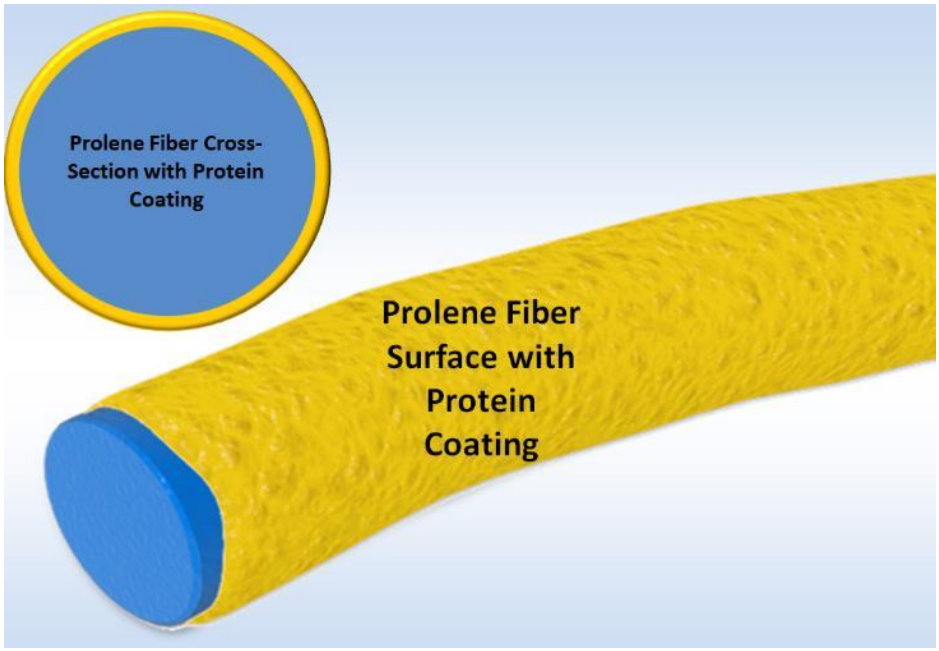
In summary, the well-known reaction of proteins and formaldehyde produces a hard, brittle, insoluble crosslinked polymer that defines the basis of flesh "fixation" long known and used by histologists and pathologists. However, as noted, the formaldehyde-protein polymer is extremely difficult to remove from mesh fibers. Therefore, interpretation of much of the printed analytical data derived from formalin-treated explants is suspect and, frankly, unreliable unless consideration is given to the presence of fixed proteins, as well as an appropriate cleaning protocol.

Figure 11 illustrates the protein-formaldehyde encapsulation of Prolene fibers and subsequent cracking of the protein-formaldehyde shell surrounding the fibers.

a) A pristine Prolene fiber used in Ethicon's mesh.



b) After the pristine, Prolene mesh is implanted, within milliseconds protein coatings immediately form around and through the mesh.[93]



c) The Explanted Mesh with protein coating attached is placed in a formalin (formaldehyde) solution. The Formaldehyde-Protein Fixation Chemical Reaction

begins and continues for as long as the mesh is in formalin. The formed and crosslinked adsorbed protein coating is brittle, insoluble and hard. The brittle and hard casing around the Prolene fiber will crack with drying and/or physical manipulation.

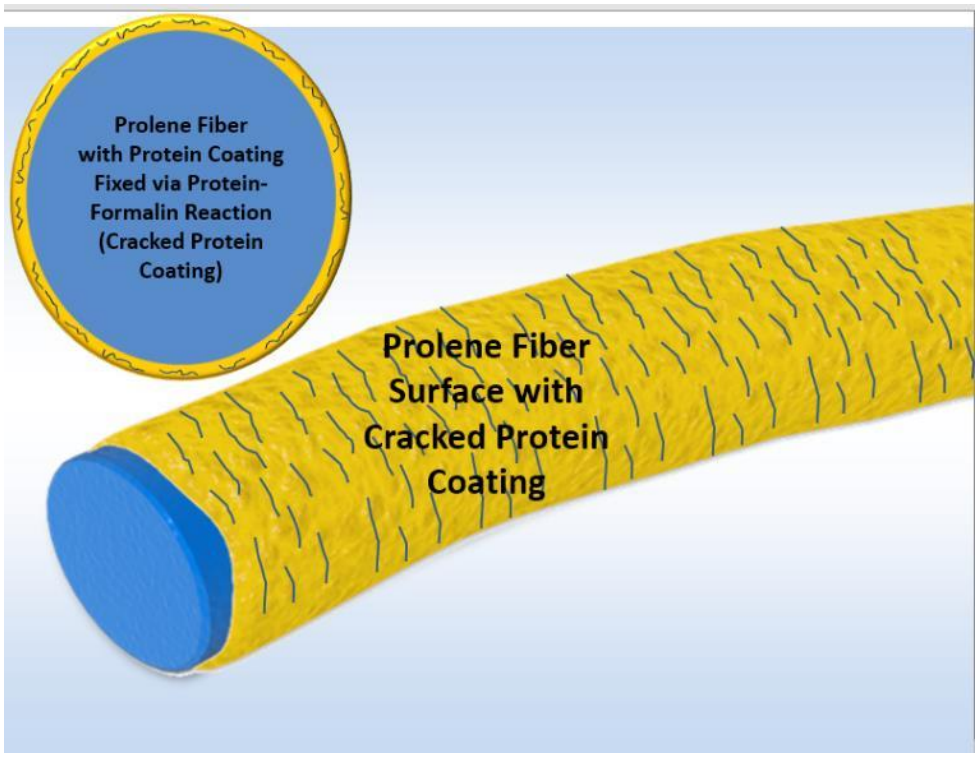


Figure 11. Protein-formaldehyde encapsulation of Prolene fibers and subsequent cracking of the crosslinked protein-formaldehyde shell.

The writings of others, as noted by Iakovlev[94], including but not limited to the work of Costello *et al*.[95], have claimed, without definitive scientific evidence, that explanted PP degraded to the extent its intended use has been compromised. For instance, Costello boldly concluded that "…explanted PP meshes did undergo degradation while *in vivo*…" Clavé further clouds the issue of PP stability with his manuscript titled "*Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants*".[96] Costello's statements are misleading in that he had no analytical data supportive of his conclusion, which was "The studies provide evidence contrary to published literature characterizing PP as inert in such applications." Furthermore, Clavé purports to perform DSC to identify *in vivo* changes or "degradation" of PP via changes in glass transition temperature (T_g), melting temperature, and heat of fusion. However, he goes on to report DSC thermograms of what he referred to as treated, degraded, and non-degraded LDPPMF (low density polypropylene multi-filament) explants were all similar to treated pristine Prolene. Additionally, his experimental evidence via DSC thermo-grams of so-called "degraded" and non-degraded HDPPMF (high density polypropylene multi-filament) explants were reported as being similar to those of the treated, pristine, Prolene samples.[97] It is inconsistent with scientific principles for Clavé to suggest that

degraded, non-degraded, and pristine Prolene all possess similar DSC thermograms. There would be definable and explainable differences in these very important polymer properties had degradation occurred. Furthermore, he states that no modifications were observed in the melting temperature or heat of fusion of these samples. However, the presence of structural modifications (i.e. degradation) or material impurities, if they exist, (i.e. presence of degradation products) will alter melting point and heat of fusion values.[98] Clavé writes that, "Thus, if oxidation occurs in these prosthetics, it takes place in the amorphous zones, and crystallinity is preserved."[99] However, there is no scientific evidence that any scientifically significant oxidation of Prolene occurs *in vivo*.

FTIR Data

The use of Fourier Transform Infrared (FTIR) spectroscopy is, for the most part, an analytical tool of qualitative analysis. In the following discussion, I will focus on frequency assignments as they relate to functional groups, such as carbonyl groups (C=O). It should be noted that the strong frequencies at 1539, 1653, and 3300 cm^{-1} are indicative of protein(s) and not PP and/or Prolene.[100] In lay terms, each molecular species possesses an FTIR absorption unique to that molecule; much like fingerprints of humans.[101] Each human is said to possess a unique fingerprint, the reason fingerprint data is forensically used to determine human identification. However, in identifying molecular species or chemical structures via infra-red spectroscopy, it is necessary to establish the "fingerprint" for the specific molecules to be studied; just like it is necessary to take a human's fingerprint and store data in a file for subsequent "matching" should the need arise. The presence of absorption frequencies, as well as the absence of same, are instructive in confirming sample identification.

Other plaintiff's experts have often made no effort to remove adsorbed formalin-fixed protein from explanted samples prior to evaluation. Thus proteins would be expected to be present on the explant samples. It is instructive to remember that all explant samples discussed herein were "fixed" in formaldehyde.

One must then ask the question, if proof for oxidation of Prolene is the presence of carbonyl bands or frequencies, accompanied by loss of molecular weight, how can one knowledgeable in the field continue to espouse oxidation when no carbonyl band exists and molecular weight loss has not occurred?

Consider the following: carbonyl bands are structural entities possessing carbon and oxygen (C=O) and are indicative of oxidation when they form from a molecule made of only carbon and hydrogen, as is PP. Stuart states in her text, "Carbonyl stretching is one of the easiest absorptions to recognize in an infrared spectrum." It is usually the most intense band in the spectrum, and depending on the type of C=O bond, occurs in the 1830 – 1650 cm^{-1} region."[102] Indeed, my experience as a scientist has shown that to be true. By way of example, examine the Reference Spectrum (Figure 12) for Polypropylene[103] and then for oxidized polypropylene (Figure 13).[104] PP does not possess a carbonyl absorption frequency as it is a molecule made of only carbon and hydrogen. Accordingly, there is no carbonyl frequency in Figure 12. However, Figure 13 is another matter, as this spectrum represents oxidized PP, wherein a carbonyl frequency is predicted to be present, and it is; see the absorption frequency at ~1740 cm^{-1} .

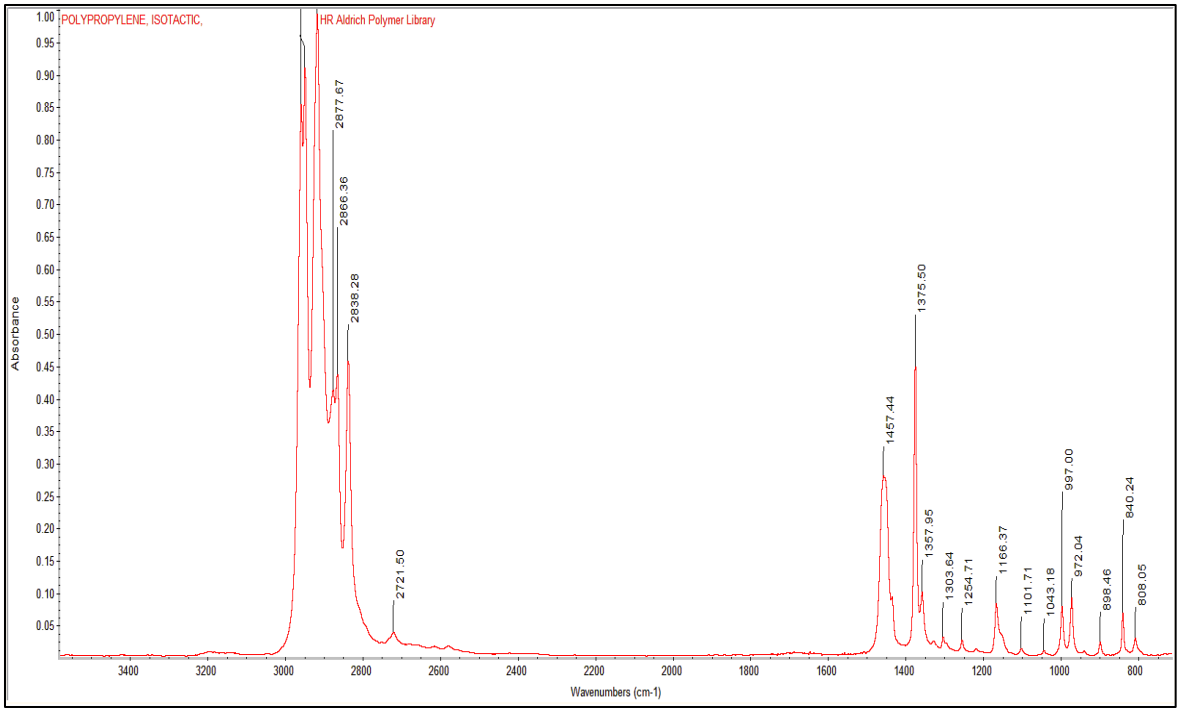


Figure 12. Reference Spectrum of Isotactic Polypropylene, HR Aldrich Polymer Library.[105]

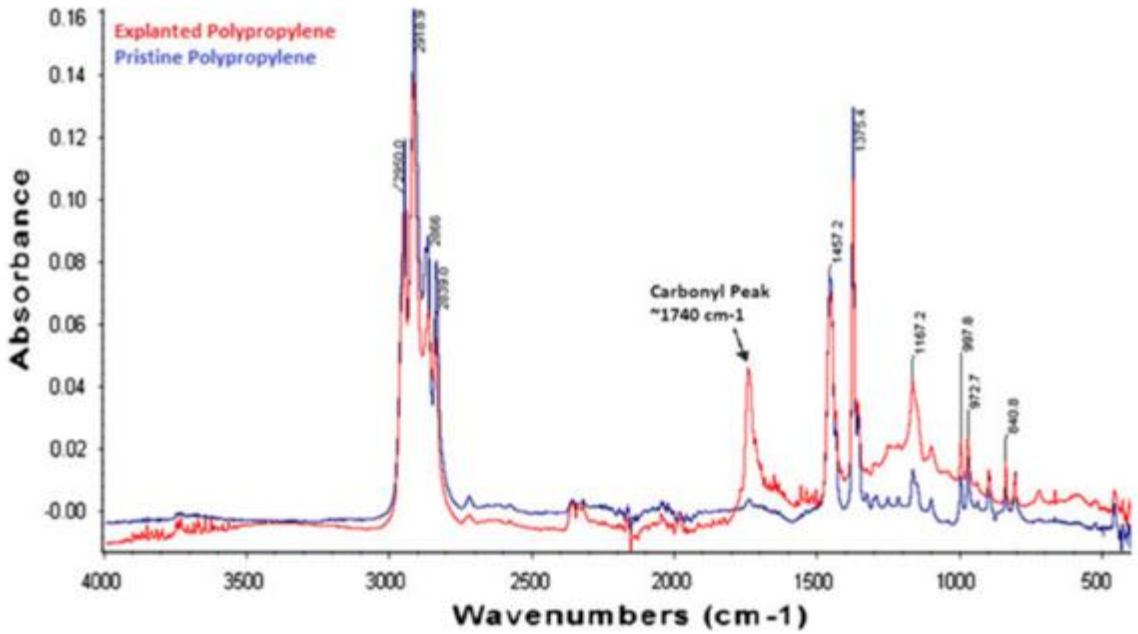


Figure 13. Referenced Spectra for Oxidized Polypropylene via Wood, *et al.*[106]

The Wood, *et al*. manuscript includes a spectrum of oxidized PP represented by a strong carbonyl, as specified by Stuart, frequency at ~1740 cm^{-1}.[107] It is important to note that the sample in the spectrum is **not** of an Ethicon device and reportedly does not contain an

antioxidant additive package.[108] It is imperative, however, that proteins possess carbonyl groups, in the form of the amide functionality (Figure 14), and amide carbonyls strongly absorb light, as they should. Figure 15 details the characteristic infrared bands of peptide linkages[109] while Figure 16 displays the FTIR spectra of collagenase, a human protein.[110]

In summary, I have not observed any FTIR data or any other evidence of scientifically significant Prolene oxidation during implantation.

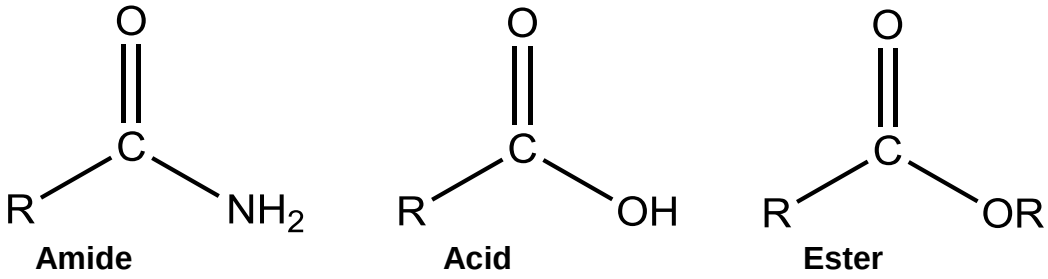


Figure 14. General structures of an Amide, Acid, and Ester

Table 1	Characteristic infrared bands of peptide linkage	
Designation	Approximate frequency (cm^{-1})	Description
Amide A	3300	NH stretching
Amide B	3100	NH stretching
Amide I	1600–1690	C=O stretching
Amide II	1480–1575	CN stretching, NH bending
Amide III	1229–1301	CN stretching, NH bending
Amide IV	625–767	OCN bending
Amide V	640–800	Out-of-plane NH bending
Amide VI	537–606	Out-of-plane C=O bending
Amide VII	200	Skeletal torsion

Figure 15. Characteristic Infrared Bands of Peptide Linkage[111]

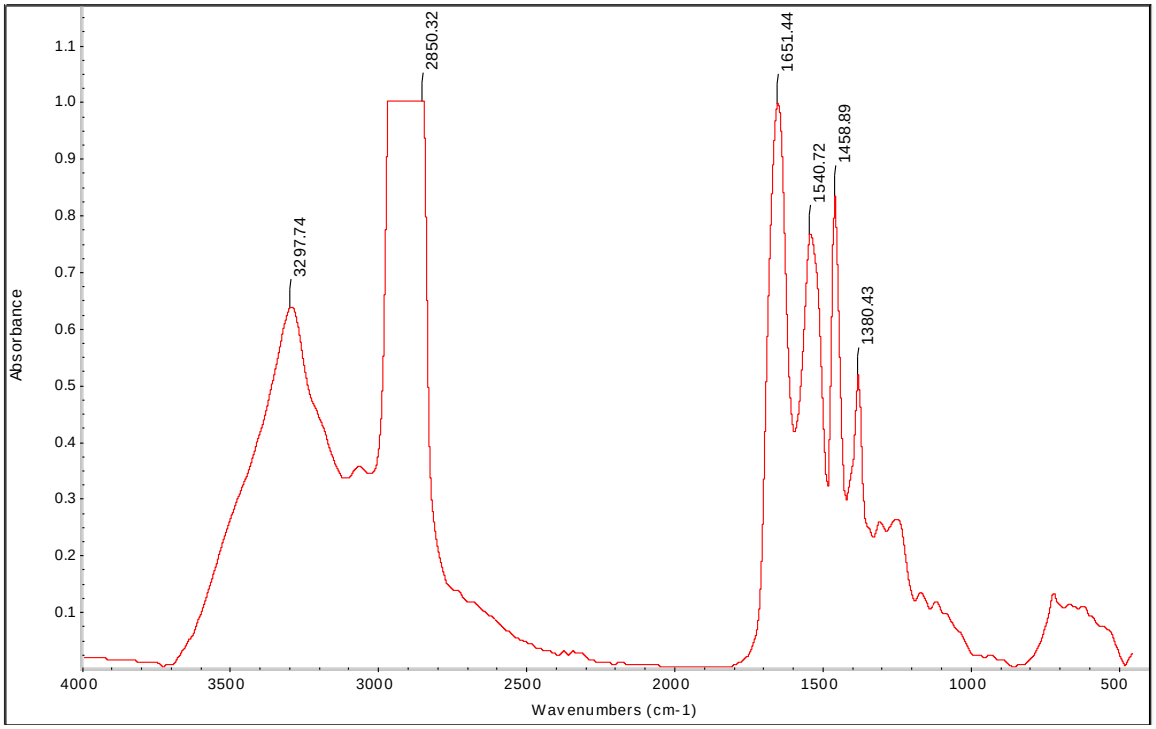


Figure 16. Collagenase (Sigma Biological Sample Library)[112]

Consider the issue of "oxidation of polypropylene." Polypropylene, and also Prolene, can oxidize under the right conditions, i.e. in ultraviolet light; a circumstance we are not dealing with in the matter at hand. Testing and analyses data are presented herein to scientifically and conclusively prove Prolene mesh does not oxidize in the body. When speaking of polypropylene oxidation, it is not unusual to note thermal condition requirements well above 150ºC (302ºF).[113] The normal body temperature is a mere 37ºC or 98.6ºF and insufficient to affect PP thermal degradation.[114] Prolene does not begin to oxidize or degrade until a temperature of 333ºC or 631ºF is reached as demonstrated by TGA analysis shown earlier in this report (Figure 4). Polypropylene, and also Prolene, exhibit excellent thermal stability well above normal body temperature.

Hydrolysis

Hydrolysis is a mechanism for molecular weight reduction of hetero-polymers, but not in the case of Prolene or polypropylene; PP is a non-hetero polymer.[115] Polypropylene is composed of main-chain, carbon-carbon atoms and it is absolutely not susceptible to hydrolysis.[116] Polypropylene's main chain carbon atoms are not polar and consequently do not attract attack by polar groups such as water. Since hydrolysis is defined as breaking apart by water and water is not attracted to PP, hydrolysis of PP does not occur. In fact, PP and Prolene are highly resistant to water and water vapor as already noted in this report.

Environmental Stress Cracking

Environmental Stress Cracking (ESC), as claimed by other plaintiff's experts in this litigation, does not cause polypropylene degradation. Fred Billmeyer, in his Textbook of Polymer Science, page 388, states "PP…is completely free from environmental stress cracking."[117] Others have also reported PP's well-known high resistance to ESC.[118,119] The authors state "It should be noted, however, that PP has excellent resistance to ESC."[120,121] They also write that "fracture of material, which is accelerated by the environment, requires crack initiation in the crazed region and subsequent fast crack propagation, and therefore a brittle failure mode" (page 206).[122] References to the work of Maier and Calafut[123] have been made by other plaintiff's experts, yet they fail to mention the treatise statements on ESC of polypropylene. The following quotes are taken from Calfut's document; "Environmental stress cracking emerges as the most prominent cause of failure in all plastics. For polypropylene, this problem can be disregarded. "A major advantage of the material is its apparently complete resistance to environmental stress cracking,"[124] and "One of the major advantages of polypropylene is its apparently complete resistance to attack by environmental stress cracking."[125]

As confirmed by my work, the explant surface (adsorbed proteinaceous matter, not polypropylene) shows cracks perpendicular to, and not oriented with the tensile stress direction. Thus, the Prolene fibers do not meet the criteria for crazing or ESC. ESC has requirements of "crack initiation in crazed region and subsequent fast propagation,"[126] neither of which has been witnessed in my work.

Neither Prolene nor PP undergo Environmental Stress Cracking.[127] Also, it is well established that fatty acids, fatty acid esters, and similar chemicals plasticize PP and improve its toughness.[128,129] D. Tripathi in Practical Guide to Polypropylene states "PP is virtually free from environmental stress cracking (ESC) observed in other polymers and attempts in the laboratory to identify a pure ESC agent for PP have failed. Many plastics are inclined to ESC or embrittlement on prolonged contact with boiling detergent solutions. The PP components specially made for washing machines do not exhibit these disadvantages. A reflux test involving 1000 hours in boiling detergent solution is used to measure water absorption, embrittling, and change of the dimension. It has been reported that suitable grades show 0.5% higher water absorption than the normal grades when soaked in detergent solution. Furthermore, no embrittlement is observed and the yield stress, ultimate tensile strength, dimensions, surface hardness, rigidity and toughness of PP are not changed."[130]

There is no evidence to support ESC in any of the Prolene mesh explants that I have examined or for PP for that matter. ESC, if it occurred, would dictate fiber rupture, loss in tensile strength, loss of elongation, loss in toughness, and loss in molecular weight, all of which are unsupported by scientific evidence/data.

Molecular weight and degradation

The work of Wypych, in the **Handbook of Material Weathering**, made it perfectly clear that oxidation (or degradation) of PP is accompanied by an increase in carbonyl concentration and an accompanying decrease in molecular weight, due to "chain scission" in surface layers.[131] The two effects simply follow each other, one cannot happen without the other happening. Supporting this tenet is the work of Zweifel, *et al.* in the **Plastic Additives Handbook** who summarized changes in material properties during polymer aging, i.e. as degradation occurs, mechanical failures increase, molecular weight changes, molecular weight distribution changes,

carbonyl increases occur, along with a rapid increase in hydroperoxide formation and a fast oxygen uptake.[132] They identify "the most important propagation reaction leading to chain scission of the macromolecule is the so-called beta-scission reaction of the alkoxy radical." This reaction, of course, leads to extensive carbonyl formation, which if present, is readily observed by FTIR spectroscopy.

Fayolle, *et al*., in "Polymer Degradation and Stability, 2000 wrote in the manuscript titled Oxidation induced embrittlement in polypropylene - a tensile testing study that PP "embrittlement occurs at a very low conversion of the chain scission process (only 1 scission per 3 initial chains) and it can be demonstrated that it results from a decrease in polymer toughness."[133] Ethicon's 7 year dog study confirmed, without doubt, that polymer toughness did not decrease, but instead improved with implantation. Clearly, given this referenced laboratory 7 year study, one cannot scientifically question the issue of Prolene's *in vivo* stability.

Yakimets, *et al*. in Elsevier's Journal Polymer Degradation and Stability, 86 (2004), pages 59-67 studied the "Effect of photo-oxidation cracks on behavior of thick polypropylene samples."[134] They found that "this kind of aging generally leads to an embrittlement of polymer materials. It causes a dramatic effect on the mechanical properties and fracture behaviour" as noted if Figure 17 below. None of which has been confirmed for Prolene.

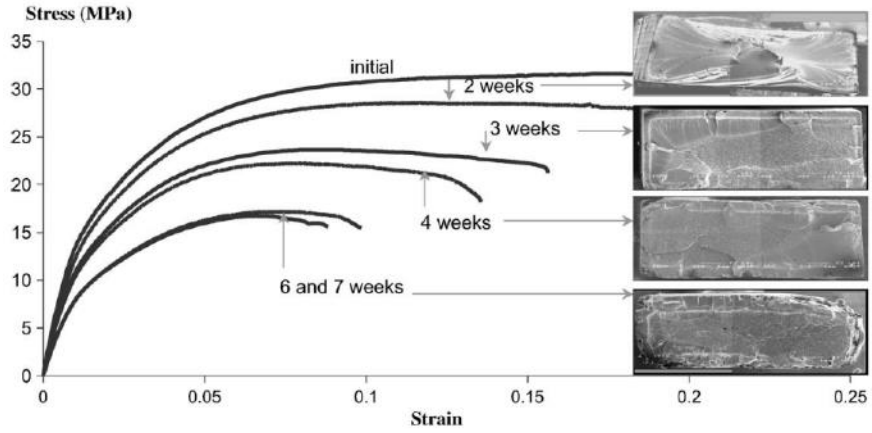


Figure 17. Stress-strain plot as a function of aging time.[135]

Scheirs writes in Compositional Failure Analysis of Polymers; a practical approach that polymer oxidation leads to loss in molecular weight and subsequent embrittlement/cracking.[136] No one, to my knowledge, has shown any meaningful changes in Prolene mesh's molecular weight during implantation. Thus, it can be stated to a reasonable degree of scientific certainty that Prolene did not undergo any scientifically meaningful degradation in the 7 year dog study.

I have reviewed Dr. Jordi's testimony regarding molecular weight analysis of more than 15 samples characterized via high-temperature GPC (HT-GPC). These analysis and molecular weight data were reported by plaintiffs' expert, Dr. Howard Jordi, and I rely on the results included in his Final Report of May 20, 2014. Dr. Jordi states on page 6 that "oxidative degradation can alter its molecular weight and polydispersity index (PDI) through cleavage of the long polypropylene chains into smaller fragments."[137] It is instructive and very significant,

however, that his reported data does not support loss of molecular weight during implantation, or that Prolene is oxidized *in vivo*.

The Jordi report listed depolymerization as a means of oxidizing or reducing the molecular weight of polypropylene. Depolymerization, by the very context of the word, de-polymerization, is the opposite of polymerization. The former reduced the molecular weight while the latter increases molecular weight. Indeed, if depolymerization occurs in Ethicon's mesh products or any other polymeric products, a loss in molecular weight will occur. Quite simply, the original molecule will become smaller, and weigh less, because its polymer chain was broken into two or more smaller, individual molecules.

Gahleitner and Fiebig write that "In contrast to other polyolefins, such as PE (polyethylene) or most olefin-elastomers (EPR, ethylene propylene diene rubber (EPDM), radical reactions in PP cause mainly a degradation effect, reducing the average chain length of the polymer and especially affecting the high molecular weight fraction---a significant reduction of mechanical properties can be expected. The normal consequence is embrittlement, a massive decrease in toughness."[138] Therefore, if there is oxidation or other degradation forces upon Prolene mesh fibers causing molecular weight loss, it is clear and obvious that reductions in molecular weight will significantly adversely affect physical properties of the mesh products or, for that matter, any polymeric product. Consider the facts/data, however, where in the current matter it was shown by two investigators, Daniel F. Burkley, an Ethicon employee, and Dr. Howard Jordi, founder of Jordi Labs and plaintiffs' expert, that property altering molecular weight changes did not occur *in vivo.* Thus, there was no evidence of any scientifically significant Prolene degradation. Furthermore, the excellent physical properties obtained by Burkley from the explanted sutures of his 7 year dog study is consistent with no significant or property altering molecular weight of Prolene, and is additional data confirming Prolene does not meaningfully degrade *in-vivo*.

In Burkley's study, wherein he selected six samples from four dogs, there were no significant changes in molecular weight for any of the polypropylene suture materials after 7 years of implantation.[139,140] Furthermore, Dr. Jordi performed molecular weight determinations on TVT products that contain the same material in the product at issue in this case; both pristine TVT and explanted devices from more than 15 patients.[141] Like Burkley, Dr. Jordi wrote "The Jordi GPC analysis of both control and explant samples tend to confirm "The 7 year Dog Study" performed at Ethicon referred to as Exhibit T-2182 in his (Burkley's) deposition of May 22, 2013, in that little to no macro Mw degradation was noted."[142] In other words, both Burkley and Jordi independently determined unequivocally that there is no evidence of scientifically significant Prolene degradation (no meaningful MW loss) *in vivo*. Therefore, no meaningful degradation of Prolene occurs in-vivo, as molecular weight loss is a form of degradation, i.e. no meaningful degradation, no meaningful molecular weight loss.

Nanothermal Analysis

I have also reviewed Dr. Jordi's nanothermal analysis data in his report based on his prior analysis in the Diane Bellew matter. Nanothermal analysis allows one to select sample locations at which they wish to investigate surface thermal properties on a nano-scale (10^{-9}). The thermal probes utilized are very small, i.e. again on the nanoscale, and thus very small sample areas are heated, from which thermal data is collected. The end radius of the probe tip

contacting the surface for nano-analysis is only approximately 30 nanometers in width (Jordi Bellew Report, page 76). Consider for example the Jordi data of Fig. 80 which is a Nanothermal spectra provided for the Bellew explant, and covered a distance of only 10 microns in width and 1 micron in depth. In keeping with this comparisons, Fig. 81 covers a width of approximately 1/7 that of a human hair and a depth of 1/69 that of a human hair. Thus, the question should be posed, can a depression of only 1 micron truly be defined as a "crack?" For instance, and by way of comparison, we have shown the thickness of a human hair measured 69 microns. Manufacturers of the Nano-thermal units have shown surface profiles of clean glass measuring 0.8 microns as noted in Figure 19 below.[143] In addition, we have shown in our work the thickness of the Protein-formaldehyde composite measured 3.15 microns.[144]

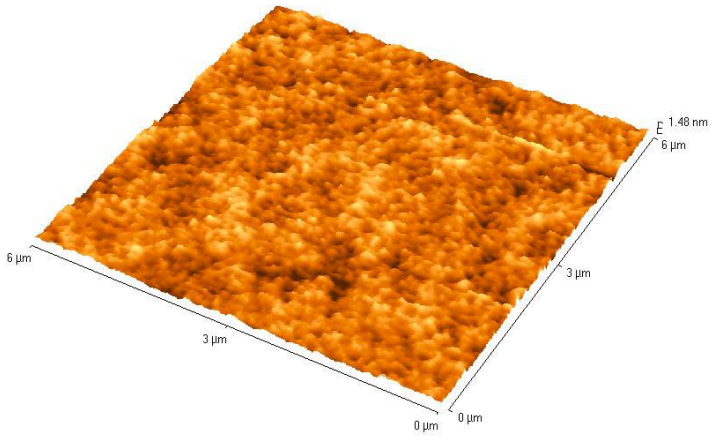


Figure 18. Clean glass surface: roughness ~0.8 nm[145]

The Jordi Report provides melting point data taken via the Nano-thermal AFM unit (see Figs. 78, 81,82, 83) and states that the lowering of melting points via nanothermal analysis as opposed to DSC data (Jordi Bellew Report, page 84, 3rd paragraph) confirm oxidation occurs on the surfaces of Dianne Bellew's explants.

What Dr. Jordi does not say, however, is that Prolene is a semi-crystalline material, with amorphous and crystalline regions, and regions of transition from amorphous to crystalline. Neither does he say that he cannot prove or identify which are the regions, i.e. amorphous or crystalline, from which he is taking and recording melting point measurements (see Fig. 83). Neither does he write that the Bellew's B explant has not been cleaned of tissue with any chemical reagents and thus residual fats, fatty acids, fatty acid esters, cholesterol, and the like remain as contaminants on the Bellew B explant. Each one of whose presence will have a lowering effect on melting point.

Finally, surface compositions have not been scientifically determined for any of the nano-thermal AFM samples. Consider the following statement for example, "For the analysis of sample Bellew, Dianne B regions that were not covered in tissue material were chosen for AFM and nanoTA measurements can be seen from the optical image shown in Figure 79, the surface of the fiber is significantly different from that of the exemplar fiber, with cracks visible across the length of the entire fiber." (Jordi Bellew Report, page 79). The Fig. 79 reference comparison to exemplar fiber at Fig. 78 is inappropriate for a scientific comparison,

and does not allow one to determine if materials are present on the fiber, and if so, what their compositions are.

It is inappropriate and scientifically unfounded to make the following statement, "Bellew, Dianne C treated with hypochlorite were also examined with AFM imaging and nanoTA. As can be seen from the AFM image in **Figure 83** (left), there is a significant difference surface morphology between the Bellew, Dianne B and Bellew, Dianne C fibers with large flakes of material visible on the surface of the hypochlorite treated Bellew fibers." (Jordi Bellew Report, page 82).

To speak of "large flakes" when describing nano-spatial relationships is non-scientific, confusing, and misleading.

The nanothermal analysis data as presented by Jordi wherein he states, "…the nanothermal analysis data in the current Bellew report (discussed below) clearly shows a vast difference between melt temperatures at the surface of the Bellew sample (121-127°C) compared to that of the exemplar (176°C)." (Jordi Bellew Report, page 10) However, at face value this is misleading in that a single data point (121-127°C) was selected on an un-cleaned explant, with no indication of surface contamination or amounts of contaminants, in contrast to the clean and unused exemplar (176°C).

The Jordi data does not accommodate determination of surface composition(s) of any of the Jordi Report AFM samples. Neither can the data collection location, nor surface contaminants be identified at data collection points. Moreover, the AFM data included in the Jordi Bellew report must be confined to 1 micron of the outermost film surface according to Dr. Jordi. (Jordi Bellew Report, pages 10-11).

The Jordi Bellew Report established that surface morphology for the Bellew Explant can be described in the following way:

1. Surface morphology is restricted to 1 micron depth, essentially the same surface profile as a piece of smooth glass

2. Surface morphology confirms no crack propagation

3. Surface morphology confirms no, surface or otherwise, degradation of the Bellew explant.

4. Surface morphology does not control nor otherwise have an effect on overall fiber properties and thus performance.

5. Surface morphology offers no evidence of any type that could be described as ESC and thus allegations for same are totally unfounded and not supported by any scientific and factual data. (Jordi Bellew Report, page 55).

Microcracking and related studies

I have received a number of documents dealing with alleged Prolene "cracking" and circumstances surrounding this supposed phenomenon as suggested by plaintiffs' experts in this litigation. Accordingly, I will discuss a number of these documents below:

1. ETH.MESH 12831405 June 15, 1982 memorandum discussed cardiovascular and ophthalmic implants. Crack depths were measured but lack of precision was evident with a stated +/- 50% estimate of depth for the ophthalmic implants. Edge on views of cracks for the cardiovascular explants varied from 2 to 4.5 microns. There was no study or effort to identity the cracked material. The depth of cracks and the measurement precision noted above contributes little to the issue. Thus, with no identity of the composition of the cracked area the data has little significance to the topic at hand.

2. ETH.MESH 00006313-6314 by Emil Brysko, Ph.D. titled "Examination of 5/0 and 6/0 Cardiovascular Prolene Sutures Explanted after 2 to 6 years Implantation" was reviewed. This study used 9 explants, 3 were stored wet in formalin and 6 were allowed to dry and were evaluated dry. No tissue was removed from any of the explants.

Wet samples were evaluated for cracking, then allowed to dry and reexamined. It is significant, but not surprising, that wet samples at 2, 3, and 6 years were essentially crack-free. The 3 year sample was reported to have "barely visible cracks in small area."

Two of the dried and three two year explants exhibited cracks while one had no cracks.

A dry, 4 yr. explant was cracked; and two of the three year dried explants were cracked while the wet 3 year implant was not cracked.

Finally, the 5.5 yr. dried explant was cracked, as was two dried 6 year explants. However, the remaining wet six year explant was not cracked. The conclusion was that "sutures kept in the wet state do not crack."

It was also stated that a wet, non-cracked sample was observed to begin to crack while it was drying. This observation involved a non-cracked, wet explant being placed on a microscope stage and "cracking was actually observed by drying." These data are totally consistent with the tenet that cracked material noted by SEM and OM is not Prolene but rather tissue and or protein-formaldehyde polymer formed during the flesh "fixation" process. For instance, Prolene is hydrophobic, as it is 100 percent hydrocarbon and hydrocarbons do not dissolve in water. Thus, Prolene does not absorb water, and nor does it swell in water to the extent it would crack during a drying off process. The material cracking upon drying is clearly hydrophilic, and when wet, imbibes water and swells. When the drying process begins the tissue/protein-formaldehyde polymer contracts during water loss, becomes brittle and cracking ensues. Hydrophobic Prolene would not, and cannot by its chemical composition, react to the presence of water loss as described.

3. ETH.MESH 00006309 BY Matlaga, Sheffield, and Fetter on May 25, 1983 described the evaluation of an explant suture obtained from Dr. Gregory. The explant was a Prolene vascular graft fixed in formalin. The explant was removed after 3.8 yrs. implantation time, and kept in formalin for approximately 6 weeks prior to analyses. Three of the explanted suture samples were subjected to tensile strength measurement with an 80% retention of tensile strength value compared to a control suture. This is not surprising given the Burkley study showed a decrease in tensile strength after implantation but with increases in elongation, a physical property manifestation leading to an increase in suture toughness with implantation time. Matalaga, *et al*. did not report elongation values. Thus, while a portion of the data as reported is consistent with the Burkley study, it is insufficient to be meaningful in arriving at a final conclusion regarding physical properties of the explanted Prolene.

4. ETH.MESH 00006312 of Nov. 7, 1984 investigated the status of a 7 year ophthalmological explant. The memorandum speaks to wet and dry states so it is unclear as to whether the explant was received wet or was dry and tested wet. It is therefore difficult to draw any conclusion from these data regarding origin of cracking, if same existed.

5. ETH.MESH00006310 by Franklin Schiller on Sept. 27, 1984 reports on a Prolene suture removed from an eye after 7 years implantation. The explant was fixed in glutaraldehyde and thus the protein-aldehyde fixation reaction took place. The sample, with no noted cleaning, was viewed by SEM where cracking was observed over most of the suture surface. Given the fixation process and lack of explant cleaning, the reported result is not surprising.

6. ETH.MESH 00006386, a November 5, 1984 memorandum titled “Prolene Microcracking” reported on sutures from ophthalmic as well as cardiovascular applications. Unfortunately, there is no information on the method of fixation for any for these explants. What is interesting, however, is the statement “In severe cases, the cracks lead to the production of a separated layer of seemingly uniform thickness and a relatively clean surface underneath.” These observations strongly suggest fixation in formaldehyde with subsequent protein-formaldehyde polymer formation, and thus the uniform thickness and a relatively clean surface (Prolene) underneath. It is significant two distinct layers were noted, “a separated layer,” and a “relatively clean surface underneath.” If the viewed surfaces were Prolene in origin, there would not have been a driving force for two distinct layers, as they would have been material of like composition.

7. ETH.MESH 00006304 study titled “Fourier Transform-Infrared Examination of Prolene Microcrack and Photo-Oxidized Polypropylene” dated November 13, 1984 reported three methods of infrared examination and they were: 1. ATR surface examination, 2. Examination of explants on micron level with FTIR-microscopy, 3. Examination of photo-oxidized Prolene films via FTIR.

The study intent was to determine the composition of the exterior surface of cracked explants, and if treating explants with formalin for storage and attempted removal by

toluene produced artifacts in the ATR-FTIR results. Explants 83-165 and 84-194 were examined. It is unclear whether these explants were fixed in formalin but without a statement to the contrary, suggests they were. The authors note "clear evidence of protein was observed at 1660 and 1540 cm^{-1} and a band at 1714 cm^{-1}which the authors assigned to oxidized Prolene. With respect to the latter assignment, I disagree. This is the lipid or fat carbonyl absorption region.[146] Sakoda states "The extent of oxidation is usually measured by FTIR spectroscopy. However, there could be considerable error in the measurement since it is difficult to distinguish the peak derived from lipids adsorbed in UHMWPE from that from oxidation of UHMWPE."[147]

The FTIR spectra to which they refer are not available to me at this time but I am aware that the 1714 cm^{-1}region is not a protein carbonyl but an ester (lipid) or fatty acid region absorption. It is unclear why explant examination would be conducted by ATR-FTIR and serum protein would be annealed at 125^{o}C and deposited on NaCl plates for transmission FTIR, a change in obtaining FTIR spectra. Such reaction conditions are very likely to hydrolyze protein amide bonds with transformation to an ester or carboxylic acid and thus create the presence of the 1714 cm^{-1} absorption, an absorption not originally in the explant. Also, it is unclear what the author means by "ATR spectra of clean Prolene."

8. The ETH.MESH 00006325 of Dr. Peter Moy's March 11, 1985 memo and entitled "Prolene Microcrack Experiments" comments that given the many studies to understand the supposed "cracking" of explants, "only two explanted sutures have been examined in greater than cursory detail." In his attached data it was noted that aorta and heart explants *in vivo* from 1-4 years and stored in formalin had no cracks, while a vascular graft implanted for 2 years with unknown treatment showed no cracks, a 2 year vascular explant showed no cracks when wet, but during drying cracking became apparent. Abdominal explants from 3-5 years implantation and stored in formalin showed no cracking on histology slides, while a 3 year vascular graft explant stored in formalin showed some cracking. Similar results were noted for other explants with the predominance of cracking accompanied by formalin fixation.

ACC. No. 83-165, a vascular graft, implanted for 6 years and stored in formalin after explanting, provided interesting and instructive data. For instance, the formalin treated Prolene sample showed surface cracking. However, when the explant was examined wet, no cracks were evident but when the sample was dried, cracks were evident. Surface flakes were examined by FTIR and only proteins and Prolene were present and no oxidized species.

On September 30, 1987 Dan Burkley submitted a report ETH.MESH 12831391 titled "IR Microscopy of Explanted Prolene Received from Professor R. Guidoin." Samples were examined "as is" with no special preparation. He wrote "the IR spectra appeared bottomed out since the sample thickness is quite significant." This type spectral interference accompanies transmission microscopy as the incident light must travel through the sample. The thicker the sample, the poorer spectral resolution.

Burkley noted the Guidoin sample 83D035 implanted for 8 years was examined optically. The explant was scraped with a needle to obtain a waxy snow which was not conducive to FTIR spectroscopy in that form. The sample melted at 147-156 °C and stated this was the melting point range previously observed for oxidatively degraded PP. However, no data was provided to confirm how the melting point of "oxidatively degraded PP" was determined. For instance, it is well known that presence of impurities causes melting point depressions.[4] It is obvious from Fig. 10-11 that proteins are present after spectral features of moisture are subtracted, leaving Prolene and proteins with possible carboxylate ester or acid frequencies present. Burkley is clear that the 1718 cm^{-1} absorption is "a carbonyl band most likely with esters but also likely with acids." He is correct in that the 1718 cm^{-1} frequency could as well be from calcium stearate, the flow control agent making up part of Ethicon's Prolene formulation. The 1638 cm^{-1} frequency is assigned as Amide 1 and 1618 cm^{-1} as nucleic acids or lipid absorptions. Thus, a melting point depression described by Burkley can be the result of several impurities to Prolene such as those described.

Finally, I disagree with the Burkley conclusions[148] given the following:

- There is insufficient analytical data to determine if Dilauryl Thiodipropionate (DLTDP) concentration is decreased in explanted sutures. Certainly the durability data that has characterized Prolene's use in the human body for more than 50 years does not support DLTDP insufficiency. Neither does Burkley's dog study. Simply put, there is no proof that Prolene meaningfully degrades and/or oxidizes in the human body; given these data and common sense, DLTDP and Santonox R are certainly performing their prescribed duty as formulation ingredients and, therefore, must be present and in sufficient quantities. One has only to review the excellent physical property data; i.e. tensile strength, elongation, modulus and toughness to confirm the long term efficacy of the Prolene stabilizer additives, DLTDP and Santonox R.

- Furthermore, plaintiffs' experts have provided analytical data proving DLTDP and Santonox R are extracted from Prolene by formalin, and we have brought that to light in our report(s). Burkley's pristine sample was never in contact with formalin and, thus, DLTDP and Santonox R could not be removed by formalin solvation. Furthermore, Burkley's explanted sutures contained fatty materials and proteins as shown by FTIR spectra, all of whose presence would minimizes the concentration of DLTDP and, thus, its spectral presence. Spectral absorptions vary depending on a molecule's environment and the method of analysis, i.e. transmission microscopy, reflectance microscopy, and ATR spectroscopy.[149,150]

- Proteins are present in the spectra of explanted sutures. I call attention to Figures 10-11 and absorption frequencies in the 1600 cm^{-1} range as well as the 3300-3400 cm^{-1} region. Both are indicative of proteins. Consider the Table I statement (ETH.MESH 12831393) "the broad nature of this band (3409 cm^{-1}), along with its position suggests a primary amine…" Proteins possess primary amine functionality and thus further confirmation for protein presence.

- There is no indication of oxidation. Had there been oxidation, the spectra of Figure 11 would have shown sharp and strong absorption frequencies in the 1750-1700 cm^{-1} region and no absorptions in the 3300-3400 cm^{-1} region, and there is no 1750-1700 cm^{-1} and there is absorption in the 3300-3400 cm^{-1} region.

- I have examined documents possessing no Bates stamp but numbered 76-84 and 89-100. These are data sheets holding dates, magnifications, KV, Modes, and brief explanations of explant conditions. These data are accompanied by SEM photomicrographs numbered 2348-2436 and 86TMO 045,038,007, 87TFE002,86D050,86D077/66TM044, and numerous more 86- and 87-SEM photomicrographs with magnifications as high as 5000X. While the photomicrographs speak for themselves there is no accompanying data describing their history of origin, the fixation process, the length of time in fixation, nor any other data from which meaningful scientific conclusions can be made.

Questionable Pathological Opinions

Some plaintiff's experts have incorrectly opined as to the formation of degraded 'bark' surrounding Prolene fibers. They cite this appearance as evidence of Prolene degradation. However, they incorrectly identify this layer as oxidized Prolene. I have consistently proved by LM, SEM and FTIR spectroscopy that adsorbed proteins surround Prolene fibers and their presence must be considered when performing explant analyses. Simply put, they must be removed prior to explant analysis. Otherwise, the analyst is viewing or testing a contaminated material, and not the desired species. For instance, some plaintiffs' experts misrepresent the coloration of histology slides during the Hematoxylin & Eosin (H&E) staining process. On the one hand they say that polypropylene will not stain but on the other, state that coloration observed is attributed to staining of degraded polypropylene. It is clear they do not understand the chemistry of dyeing, which controls the process from beginning to end, nor the chemistry of protein fixation. They further confuse the issue with polarization light experiments where they correctly state that both polypropylene and proteins are birefringent and thus polarize light; however, they follow these statements with attempts to identify and segregate polypropylene apart from proteins with polarized light photomicrographs.

It is basic, fundamental chemistry, and certainly basic polymer chemistry, that proteins are polymers, and formaldehyde in the presence of proteins (flesh) forms a crosslinked formaldehyde-protein polymer, i.e. the end product of the traditional "protein-fixation" process. Polypropylene, because of its chemical structure, on the other hand, is not affected by, nor reacts with formaldehyde but is surrounded by adsorbed, and consequently adhered, proteins that are "fixed" when immersed in formaldehyde. This layer of adsorbed and fixed proteins must be considered when studying or examining polypropylene explants fixed in formaldehyde. However, some plaintiffs' pathologists have not, to date, recognized the "fixed" proteins produced by their immersion in formalin. Consequently, they are unaware of the "formalin-fixation" protein product and have erroneously labelled this product as "bark."

It is likewise well known, basic chemistry, that H & E (Hematoxylin and Eosin) stains are standard stains for routine tissue evaluations. The staining process is of a chemical reaction origin. Colors are produced when, and only when, specific acid and/or base chemical reactions

occur. If a chemical reaction does not occur with H & E dyes, no color beyond that of the base dye is produced by the H&E stains. Moreover, if no chemical reaction occurs, the unbound residual stain is removed or washed away in the slide preparation process and leaves no residual stain color. Consider, for example, the following chemical reactions required for H & E stains to generate color when histological slides are processed; as illustrated in Figure 19 below.

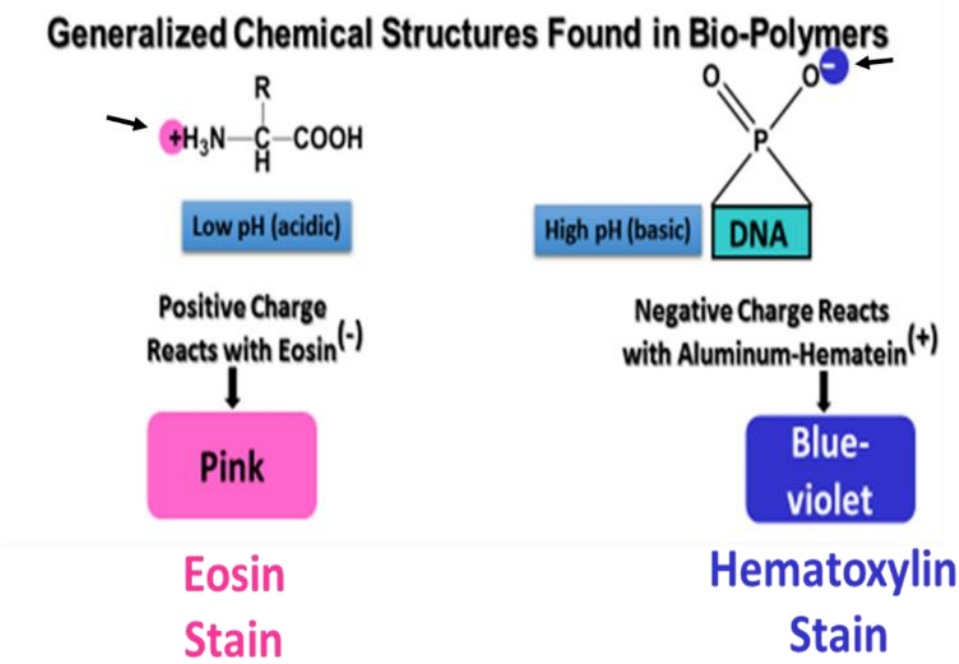


Figure 19. Chemical reactions required for histological staining by H & E dyes

By way of explanation, Hematoxylin combined with an aluminum "mordant" produces a metallic complex or "lake" holding a strong positive (+) charge. The + charged "lake" binds selectively to the negative charged (-) groups of DNA-phosphoric acid complexes.

Thus, the H & E stain turns to a dark-blue or violet color when chemically bound to substances such as DNA/RNA. These nucleic acid building blocks form salts with basic dyes, and therefore, dyes like Hematoxylin will chemically react with their negative charge to form an ionic bond, thereby staining them violet.

Eosin, on the other hand, is a negatively (-) charged anionic dye (acid salt) and will chemically react only with, and bond to a positively (+) charged group. Consequently, at a pH below 6, proteins manifest a positive charge and form an ionic bond with the negative charged Eosin.[151] Eosin is a red or pink stain, and consequently, Eosin binds to amino acids/proteins and stains them pink.

In summary, while proteins (flesh) chemically react with H & E stains, polypropylene does not, and cannot, due to its chemical composition. Polypropylene has no charged sites or pH, thus it has neither acidic nor basic characteristics. Simply put, the chemistry of polypropylene does not

allow it to react with H & E stains and thus polypropylene is NOT stained by H&E dyes as noted in Figure 20.

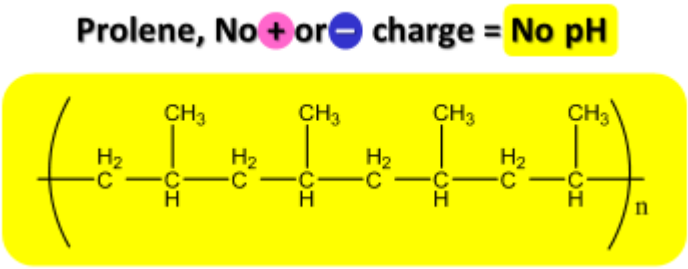


Figure 20. Prolene (polypropylene) chemical structure

However, some plaintiffs' pathologists have consistently ignored the chemistry of H&E staining as well as trichrome and other stains. Rather than assign color development based on the aforementioned scientific principles, and as stated, well known chemistry, plaintiffs' pathologists mis-assign color development, and thus assign substrate identification on the basis of substrate porosity and nanostructure. They give no consideration to well-known and established chemical principles of staining via chemical bonding of stains to substrates in order to achieve color.

Proof that Prolene fibers do not stain is provided in the expert report of Dr. Steven MacLean of Exponent Laboratories[152] which I rely upon and incorporate herein. It is my custom and practice to rely on this type report and information in reaching scientific conclusions. In Dr. MacLean's experiments, Prolene mesh was placed in oxidizing environments by exposure to UV light and, in a separate experiment, by the $CoCl_2/H_2O_2$ methodology used by Dr. Scott Guelcher. Neither of the samples accepted, and thus were not stained by the H&E dye.

Response to opinions of Dr. Vladimir Iakovlev

This section will discuss my opinions regarding those of Dr. Iakovlev after reviewing his reports in other mesh litigation regarding Prolene mesh material, including those for the Huskey/Edwards, Bellew, Corbet, Patient 3, Iholts, Clowe, and Patient 4 cases, and his various depositions.

The March 18, 2014 Iakovlev deposition confirmed no qualitative, nor quantitative chemical analyses were performed to determine the chemical composition of mesh or any other chemical species for which he offers opinions. For instance, he states on page 209 (March 18, 2014 deposition)[153]:

> Q: The degradation analysis you did regarding Mrs. Edwards' mesh was an analysis done with microscope, correct?
> A: "I detected. It wasn't analysis."

On pages 217 and 218 he readily admits that the Edwards' explant had protein adhered to it by the following statements:

Line 25, page 217: Iakovlev's statement, "Human tissue is mostly protein."
Lines 7 and 8, page 218 he states upon questioning,

Q: and this human tissue contains protein, right?
A: yes
Q: it was exposed to the formalin with the tissue on it, correct?
A: “it” meaning mesh, yes.

Consequently, formalin-fixation of proteins did occur on Ms. Edward’s explant, and accordingly the hard, brittle, and insoluble formalin-protein fixation product was formed, but was given absolutely no consideration by Iakovlev (see page 38 of this report).

The Iakovlev report of June 4, 2014 in the NJ TVT cases (page 2) states,

> Statement: “Another example of a specific finding is polypropylene degradation. The degradation material shows changed physical properties-cracking, and chemical products are released during the degradation process.”[154]
>
> Response: Iakovlev provides neither reference(s) nor reliable scientific data of any kind to support his so called degradation theory. Neither does he possess nor does he provide scientifically reliable references or data to support his contention of changed physical properties-cracking. He does not characterize nor identify any so called degradation products or “chemical products that are being released during the degradation process.” Consider the statements made and the lack of data supporting same; i.e. the following excerpts taken from his direct examination in the matter of Amal Eghnayem v. Boston Scientific Corp.: [155]
>
> Page 85
> This is the identifier of St. Michael's Hospital. It was
> received in a formalin jar
>
> Page 86
> Q. Are you familiar with the term "loss of elasticity"?
> A. Yes.
> Q. What does that mean?
> A. It means that the materials not elastic anymore. It's not
> stretchable.
> Q. What can you tell from your gross evaluation of the
> posterior mesh about the loss of elasticity?
> A. There was no stretchability of this tissue with the mesh.
> I couldn't stretch it
>
> Or
>
> Page 87
> I -- it also exhibited quite a bit of resistance on
> bending. It was stiff as a plastic.
>
> Pages 88- 89
> Q. What about loss of elasticity? What did your evaluation of

1 the anterior mesh tell you about that on Ms. Eghnayem?
2 A. They were not stretchable. They felt like plastic.

Iakovlev neither offers nor provides any quantitative or analytical data to support his erroneous and sweeping statements. He comments that "They felt like plastic," and indeed Prolene is a plastic and it is well known that it is a flexible and strong plastic. This was scientifically and experimentally established by Burkley's 7 year dog study. Thus, his claims are scientifically unreliable and lack credibility. Moreover, Iakovlev readily admits in an August 12, 2014 deposition that he is "…not a materials scientist" (page 123, line 10), yet he opines on matters that are clearly material science.[156] He speaks of plastics in a generic sense and apparently does not appreciate "plastic" is used to include literally thousands of polymeric products, some soft, rigid, and all "in-between" properties. Elongation, modulus, elasticity, brittleness, hardness, are quantifiable properties determined by via appropriate, and well established, testing methods. Consider, for instance, the ASTM methods for determining, hardness, brittleness, elasticity, elongation and tensile properties:

> ASTM D638 Standard Test Method for Tensile Properties of Plastics, ASTM D2240 Standard Test Method for Rubber Property – Durometer Hardness, ASTM D2137 Standard Test Methods for Rubber Property - Brittleness Point of Flexible Polymers and Coated Fabrics.

It is absolutely critical that any professional taking on the responsibility of evaluating explanted mesh properties, whether biological, chemical, or mechanical, possess knowledge and understanding of the process for formalin fixation (see pages 15-21 of this report). Formalin fixation has been known and practiced by the medical community, and particularly histologists and pathologists, since 1949. Rarely are medical explants not "fixed" in formalin (an aqueous mixture of formaldehyde). And in those matters, all explants were fixed in formalin by the surgeon at time of explanting (see Iakovlev's deposition, pages 27 lines 15-20 and 28, lines 6-7.)[157,158]

When questioned about the technique for measuring stiffness, Iakovlev admits it was performed by palpation. However, Iakovlev gave essentially no consideration to the phenomenon of tissue "fixation" in formaldehyde and its effect on tissue stiffness and other properties. The "fixation" process begins in the operating room with the surgeon placing explanted tissue immediately upon extraction into a formalin solution. The ensuing chemical reactions, defined as "fixation," fulfill their purpose by transforming explanted tissue (proteins) into a hard, stiff, polymeric composition of formaldehyde and proteins as described by Dr. Susan Lester[159] Formaldehyde hardens proteins and makes them water resistant.[160] The hard, brittle crosslinked formaldehyde polymer forms and in doing so, "fixes" or transforms the explanted tissue into a rigid mass, as is its primary purpose. Explanted tissue must be "fixed" or transformed into a hard, stiff or otherwise brittle state for tissue slicing by a pathologist. If no "fixation" occurred, explanted tissue would simply be too soft to affect smooth tissue cuts required for histological evaluations. Thus, explant "fixation" produces a polymeric shell, or "bark" as it is called by Iakovlev, surrounding, and otherwise encasing, the fiber. There is no dispute that explants treated and fixed with formalin may be perceived as stiff via palpation (page 32, lines 9-10).[161] However, neither is there dispute by those knowledgeable in the field that fixation (protein crosslinking), accompanied by mesh shrinkage after explanting, contributes to the "feel" of stiffness. This

thesis is further confirmed via Iakovlev who states; "The stain is showing if there is calcium in the tissue, so pretty much all fragile, brittle tissues in human body contain calcium, that's why they're brittle. I saw the bark is cracking, so my question is, is it because of calcium inclusion, and that's why I did calcium staining. And it wasn't – didn't contain any calcium."[162] (page 34, lines 4-8)." It is instructive in this matter that the "Iakovlev's so-called bark" did not contain calcium, yet the tissue was stiff. The stiffness is due to formation of a hard, brittle substance, i.e. the crosslinked "fixation" product (page 52, lines 24-25) which, given his testimony, the deponent clearly does not understand or chooses to ignore (page 54, lines 13-16; page 57, lines 1-6).[163] To further add credence to the "fixation concept" and its effects on flesh, Lester[164] in the Manual of Surgical Pathology writes:

"Ideally fixation serves to:

- Harden tissue to allow thin sectioning
- Preserve tissue
- Stabilize tissue components
- Enhance avidity for dyes
- Alter protein structure which may be crosslinked
- Shrinkage of tissue: Most fixatives cause shrinkage of the tissue. If exact measurements are important they should be taken prior to fixation.
- Over fixation may result in hard brittle tissue in some fixatives."

Tissue hardening, crosslinking, tissue shrinking, over fixation, and distortion are all by-products of the "fixation" process; a process which Iakovlev totally dismissed in his analysis.

Finally, my opinion of the deponent's lack of awareness and/or understanding – or failure to consider -- of this critical formalin "fixation" process and its effects is conclusively confirmed by his several deposition statements that follow:

See deposition, page 221 lines 9-25 and page 222 lines1-4 wherein he admits he is unsure what the term "protein polymer means."[165]

Page 221-222:

Q. You know that when formaldehyde bonds with protein polymers a new polymer is formed?

A. Please repeat the question?

Q. Sure.

Do you know that when formaldehyde bonds with protein polymers a new polymer is formed?

A. Protein polymer; I'm not sure what you mean.

Q. Okay, is that a field outside of your expertise?

A. I'm not sure if such thing exists, a protein polymer. Maybe since any sort of setting, if you accept—polymer is something with relatively homogeneous simple molecule which is being linked into continuous chains. Proteins are completely different structures. So I don't think this is a correct term."

It is basic, fundamental chemistry, and certainly basic polymer chemistry, that proteins are polymers, polypropylene is a polymer, and formaldehyde in the presence of proteins (flesh) forms another, and larger, formaldehyde-protein polymer, i.e. the end product of the "fixation" process.

See also the following quotes from Dr. Iakovlev's report for the NJ-TVT cases:

"Several observational and experimental studies showed that polypropylene used in the mesh degrades while exposed to the body environment."[166,167]

"Microscopic examination of the explanted meshes shows a layer of homogeneous material at the surface of mesh filaments (Figure 18b). The layer stains light-purple by the hematoxylin dye, while the central core of the filament does not absorb the dye."[168,169]

"Also, the material tends to adhere to the glass slide and tissue, while the central core peels off the glass slide. To investigate the nature of this material it was examined under polarized light as well as tissue was stained using immunostains for immunoglobulin and myeloperoxidase."[170,171]

Response:

The homogeneous material at the mesh surface is undeniably crosslinked formaldehyde-protein polymer to which Iakovlev gives absolutely no consideration, nor has he performed any chemical analysis to rule it out. Moreover, he readily admits that "the layer stains light purple by the Hematoxylin dye, confirming its proteinaceous nature. He further states, that the "central core of the filament does not absorb dye," and that is to be expected given the central core is Prolene. Prolene does not accept H & E dyes. Finally, his statement "Also, the material tends to adhere to the glass slide and tissue, while the central core peels off the glass slide," is certainly to be expected. The reason; Prolene has no structural features allowing it to adhere to glass, while proteins are known for their tenacious adhesion characteristics. The "fixation" chemical reaction and the products derived therefrom was established in 1948 and published in scientific literature in 1949.[172]

Thus, if proteins are attached to the surface of Prolene (and they are), and formaldehyde or formalin solution is present, it is undeniable that crosslinked protein-formaldehyde polymers form. Given formalin is a standard "fixative" in operating rooms worldwide, the remaining ingredient must be proteins for the "fixative" process to proceed. Thus, the stage is set with ideal reaction conditions for formation of the crosslinked protein-formaldehyde reaction to occur, and it does. The crosslinked protein-formaldehyde polymer readily accepts stain, while Prolene, a hydrophobic, charge neutral, hydrocarbon polymer, does not. Proteins, on the other hand, are excellent bonding agents to hydrophobic materials such as Prolene according to Schmidt who

states “Consequently, enhanced protein adsorption and conformational change are observed on hydrophobic surfaces.”[173] This statement provides a sound and logical explanation for Iakovlev’s observation that “Also, the material tends to adhere to the glass slide and tissue, while the central core (Prolene-being hydrophobic and non-polar) peels off the glass slide.” Thus, the homogeneous material at the mesh surface which Iakovlev calls “bark” is neither Prolene nor-degraded Prolene; rather it is the crosslinked formaldehyde-protein shell surrounding Prolene fibers. Furthermore, Iakovlev provides absolutely no chemical analysis of any kind to confirm the chemical composition of his so-called “bark.” He is obviously unaware that formaldehyde reacts with amines and proteins and in doing so forms a strong adhesive bond to the substrate it surrounds (Prolene); proteins are known for their tenacious adhesion.[174] This is such an important concept that the following deserves being quoted;

- “A good perspective for adoption by the novice approaching this field (*Theory and molecular mechanisms of protein adsorption*) is that all proteins adsorb to all surfaces. It is rarely a problem how to achieve the adsorption of a protein, but rather how to prevent it. Consequently, protein adsorption is the central event in the biofouling of surfaces.”
- “Surface properties have an enormous effect on the rate, the extent, and the mechanism of adsorption. Perhaps the broadest, most widely accepted generalization regarding surface properties concerns hydrophobicity and holds that the more hydrophobic the surface the greater the extent of adsorption.”
- “Also proteins are large molecular entities which usually contain many charged groups, some negative and some positive.”[175]

It is worth reiterating that the “central core” in Iakovlev’s work is Prolene; Prolene is neither acidic nor basic, it is neutral in charge, and therefore it does not, and cannot by its chemical structure, react with dyes and become colored. Moreover, the porous outer layer or “bark,” as it is called by Iakovlev, is a crosslinked formaldehyde-protein polymer, a result of the formaldehyde “fixation” process of adsorbed protein which possesses (+) and (-) charged chemical structures that readily react with H&E dyes. Iakovlev states the observed outer layer is “synthetic” which is consistent with crosslinked formaldehyde-protein polymer embedded in, and reacted with, preserved flesh.

The Iakovlev report describing experimental (ibid, page 9, last paragraph)[176] comparisons of polypropylene samples support the tenet of Prolene not meaningfully degrading *in vivo*; for instance, consider the following:

1. Mesh with 9 year *in vivo* exposure
2. Mesh with 1-year *in vivo* exposure
3. Mesh unused, new-no *in vivo* exposure

Explanted mesh samples 1 and 2 were again subjected to formalin fixation, after which they were paraffin embedded and underwent staining procedures.

RESULTS

1. 9 yr. *in vivo* exposure------detectible thicker outer layer absorbing hematoxylin dye (4-5 micron thick).

2. 1 yr. *in vivo* exposure-------thin outer layer absorbing stain-(1-2 micron thick)

3. Mesh unused, new-------no stainable layer.

Figures 18, 19a & b; 20 a & b and 21

Iakovlev makes the following statement, "The only differences I have detected so far is the thickness, where the bark with 1-year of *in-vivo is* detectably thinner than the bark of specimens of >3 years *in-vivo* exposure." (Pages 9-10). In addition, Iakovlev compares *in vivo* exposure to "degraded layer thickness" on page 10 of his Patient 3 report, stating that there is a "strong association between the bark thickness and the mesh in-vivo exposure." [177]

These data support the following explanation:

1. First, if pristine Prolene is treated with formaldehyde, no proteins are present to allow for a deposit of any kind to form on the Prolene fiber**.** Prolene alone will not react with formaldehyde to form an outer shell. Proteins must be present for formalin to react, and proteins are not present on pristine Prolene.

2. The longer implantation time, the thicker the bio-layer or protein deposition on Prolene. With extended time, there is access to more proteinaceous material for fixation, and the fixation process continues for the duration of fixation and, in the process, will "fix" more and more bio-layers of flesh. In summary, protein thickness continues to grow over time. The longer the implantation time and/or the longer the fixation time the thicker the build-up of the crosslinked formaldehyde-protein layer around the Prolene fiber surface. Thus, a nine year explant would be expected to exhibit the thickest crosslinked formaldehyde polymer shell or armor.

3. Iakovlev did not provide chemical characterization data, such as FTIR spectroscopy, to scientifically establish or prove the material adjacent or adhered to Prolene is anything other than a crosslinked formaldehyde-protein shell. However, that the shell is proteinaceous in composition was confirmed by other plaintiff's expert, and me, using FTIR spectroscopy analysis.

4. Finally, Iakovlev has not provided or used a control specimen of degraded Prolene, or PP for that matter, and scientifically proved his statement, "outer bark of degraded polypropylene absorbing dye." (Figure 19a. 9 years in-vivo exposure, page 37).

   Consider the following:

   Iakovlev has not identified or utilized a control which is known-to-be-degraded polypropylene. This is absolutely necessary in order to establish stain reaction with and thus dyeing of so called degraded polypropylene. Therefore, his statements have no support of an experimental control, nor any data that would come therefrom. Consequently, his conclusions have no merit, scientific or otherwise, or basis-in-fact and are, therefore, flawed, unreliable, and scientifically invalid**.** His thesis that Prolene, if degraded, would absorb stain, is pure

supposition with absolutely no supporting scientific data, and is inconsistent with known chemical reactions of H & E stains.

Iakovlev has used flawed methodology in developing his opinions which have no basis in fact.

5. Iakovlev's report contends the explant's outer stained layer is Prolene. Yet he has stated Prolene does accept dyes. The existence of a protein-formaldehyde polymer must be accounted for, and it is, as the stain accepting outer, porous layer of the crosslinked formaldehyde-protein polymer shell that Iakovlev incorrectly identifies as degraded polypropylene or "bark." I must emphasize polypropylene or Prolene does not accept dyes and therefore is not colored by dyes.

6. Although Iakovlev readily admits to "fixing" all explants in formalin he completely ignores the chemical product formed by the fixation process, and gives no attention to determining its presence, its composition, nor its location in his various photomicrographs. He has improperly labelled and characterized it as degraded Prolene "bark."

7. The Iakovlev report states (Ibid: page 10)[178] "The surface of the "bark" was irregular and had multiple cracks, where some cracks extended through the full "bark" thickness and either stopped at the bark-core interface or turned parallel to it (Figure 27)." If this were a scientifically valid statement, and the "bark" was indeed Prolene, one would observe crack propagation through the entire mesh fiber, and fiber breakage or rupture would be the end result. This did not occur, there was no crack propagation, and there was no Prolene degradation of the *in vivo* explants.

8. The Iakovlev report states, "Mesh degradation alters polypropylene properties." However, the report is absolutely devoid of any scientific data confirming which, if any, Prolene properties were compromised, or altered. As a matter of fact, Ethicon's 7 year dog study scientifically and unequivocally established and affirmed Prolene's physical property improvement during 7 years of implantation. Iakovlev makes no mention of the 7 year dog study.

   The Iakovlev report states, "The degraded layer has cracks showing its loss of elasticity and hardening. As a result, it introduces changes to polypropylene mechanical properties and therefore contributes to mesh deformation and hardening." Once again**,** the Iakovlev report is devoid of any scientific data to support these assertions. He has totally dismissed the teachings of Dr. Susan Lester, a pathologist, in the Manual of Surgical Pathology wherein it is stated under the topic of "Shrinkage of Tissue: Most fixatives cause shrinkage of the tissue."[179] This effect is due to molecular contraction as the formaldehyde and proteins react and lose a molecule of water in the process. The loss of water draws the two reactants closer together and thus "contraction" as a result of fixation. "If exact measurements are important they should be taken prior to

fixation."[180] Moreover, he has dismissed the work of Burkley who showed physical property enhancements of Prolene after 7 years *in vivo* implantation in dogs.[181] He has further dismissed the well-known polymer forming crosslinking reaction of formaldehyde reacted with proteins produces a hard, brittle outer shell surrounding Prolene fiber(s).

9. The Iakovlev report states (page 10) "The outer bark showed remaining blue granules in the inner parts of the bark, which further proves that the outer layer indeed originates from the filament material (Figure 24)."[182,183] It is not surprising that some blue could be seen under microscopic examination in the inner-closest layer to the Prolene fiber. Solvent softening by xylene, [184,185,186] handling, molecular contraction, manipulation and cutting of the "fixed fibers" in preparation for testing, slicing, and any other physical function could readily cause some degree of cohesive bond rupture seemingly opening up and/or softening the Prolene surface layer and appearing as an artifact. Moreover, the angle of observation can and does alter what one "sees" in the microscope objective. Finally, Iakovlev cannot distinguish between blue spots derived from H&E stains and Ethicon pigments; both are blue.

   In fact, Iakovlev testified (March 18, 2014 deposition; page 232) to the following:

   > Q: What is that? Are those spaces in connective tissue?
   >
   > A: Yes. This is just a separation during the processing. I would have to look in the microscope. But sometimes tissue gets little bit of retraction space when it's being processed, it retracts, so there's artificial empty space."
   >
   > Q: Is that what pathologist talk about when they reference artifacts from the processing?
   >
   > A: Yes, retraction, tissue retraction is an artifact.

   In this same deposition Iakovlev was questioned as to why "bark" takes up stain (page 302) to which he answered, "Why barks take the stain? It's porosity. The porous cracks, they just trap histological stains specifically." Iakovlev is likening the staining process to a physical phenomenon of being trapped in voids, rather than the well-recognized acid-base chemical reaction required for color generation.[187] This Iakovlev response is proof-positive he lacks understanding of the chemical process of staining and the required acid-base reactions. Moreover, it is well established that crosslinked formaldehyde-proteins are hard, brittle and porous and according to Iakovlev's theory they too would absorb H&E stains. Indeed they do absorb H&E stains but not because they are porous; but because they possess and hold (-) and (+) charged chemical species.

10. Finally, the very "fine, smooth, line of demarcation" between the formaldehyde-protein polymer and PP fibers (See Fig. 24a, 24b, and 24c), is indicative of two dissimilar materials.[188] H & E stains nuclei PURPLE and that is exactly what Iakovlev has shown in Figure 24c. The segment of slide he states is degraded

bark is dyed PURPLE, and consequently, by his own admission polypropylene does not stain, and therefore cannot be polypropylene. However, even in the face of his own writings, he speaks of the PURPLE layer as, "The degraded bark shows optical properties of polypropylene, however is brittle and readily separates from the non-degraded core." He has stated on numerous occasions PP cannot be dyed and this is a contradiction in fact.

Furthermore, Iakovlev fails to speak completely to Figure 24d or 24e of his Patient 3 report (page 66) which is enlightening and explanative of Figures 24a, b, and c.[189] For instance, this figure (24 d, e) provides microscopy data in regular and polarized light. He states the "degraded bark shows optical properties of polypropylene, however, it is brittle and readily separates from the non-degraded (polypropylene) core." What he fails to say is that collagen proteins are birefringent and as such possess two refractive indices, and thereby they (collagen) respond to polarized light.[190] Iakovlev confirms this on page 66 of the Patient 3 report with the statement "Note the dark collagen in the lower right."[191] In this instance, the protein coating is crosslinked with formalin. Finally, close observation of Fig. 24d (in regular light) confirms the separated and broken section between polypropylene and the remaining tissue (to the right) as showing blue-violet and well as red stain, respectively; thus confirming both are of flesh origin (not polypropylene) and are the colors one would expect from H&E staining. When this identical portion of the stained slide is subjected to polarized light, it responds to polarized light, confirming once again that proteins show the same optical properties when viewed with polarized light as polypropylene. Therefore, one cannot use polarized light to chemically distinguish between polypropylene and proteins.

Further evidence that Iakovlev's conclusions are scientifically invalid and incorrect is found in his Trichrome Stain data (see page 116, July 7, 2014 Rule 26 Expert Report of Vladimir Iakovlev).[192] Figure DB-15 of this report is titled "Appearance of the degradation bark in trichrome stain." It is instructive that:

- He assigns the red areas of the slide as "Red dye within smaller micropores of degraded polypropylene." However, the 2010 Lamar Jones Technical article in CONNECTION clearly states collagen stains blue or green depending on the collagen stain utilized (page 83) and the final staining results are: Cytoplasm, fibrin, muscle stains red, and Collagen - light green (page 84).[193] Note that Jones' assignments deal with tissue reactions. However, Iakovlev erroneously assigns the staining colors of Fig. DB15, not as tissue, but as polypropylene degradation:

  -Red as dye within smaller micropores of degraded polypropylene

  -Blue as granules retained in degradation bark, and

  -Green as dye within larger micropores of degraded polypropylene

> It is clear Iakovlev does not rely on the chemical reactions of tissue with stains, but on some sort of self-generated and undefined physical porosity, in stark contradiction to printed, technical manuscripts describing the staining process otherwise.
>
> Iakovlev's opinions and statements are based on flawed methodology. They are in direct contradiction to well established scientific principles of tissue staining. Consider the Jones Technical Bulletin titled "Mastering the Trichrome Stain."[194] Therein it is stated in the introduction section, "At the onset it must be made clear that the methods control how ionized acid dyes react with ionized basic tissues. This is the fundamental principle on which they depend and the explanation is only about how that fundamental reaction can be manipulated."[195] Following this is a statement of purpose, "The purpose of the trichrome stain is primarily to demonstrate collagen and muscle in normal tissue or to differentiate collagen and muscle in tumors."
>
> The Technical Bulletin further notes that "collagen appears white in the fresh sate, is birefringent when polarized with light" as is polypropylene.[196]

The overall discussion of mesh shrinkage in the Iakovlev report is surprisingly devoid of Dr. Lester's[197] reference regarding formalin induced tissue shrinkage and its effects on properties. I am further confused by the Iakovlev deposition description of how Prolene degradation was determined. For instance, consider pages 295 (line 24-25) and page 296 (lines 1-18) of the Iakovlev deposition. In essence, Iakovlev states proteins take up stain and that is called protein expression; he further states Prolene does not stain, given it is hydrophobic. Yet, he uses these data to conclude Prolene degradation and I see no correlation between the data he cites and Prolene degradation.[198] His opinions are contradictory and are based on flawed methodology. Simply put, human flesh made principally of proteins react with dyes and produce color, while Prolene, a hydrocarbon polymer, is amphoteric, hydrophobic, does not possess positive or negative charges and consequently does not react with dyes and therefore does not produce color. The Iakovlev report states staining is used to ascertain the amount that stain soaks up in a material and describes this as "measuring protein expression." He states stain intensity measures the amount of expression of a protein. There is no explanation of how measuring protein expression can or will determine Prolene degradation. In my view it absolutely cannot, and the Iakovlev report does not contain scientific data to support the contention that Prolene degrades in the human body. Iakovlev presents additional opinions on pages 302-303 regarding alleged degradation. Iakovlev readily agrees that: "cracked material in the surface, it can be either polypropylene crack or protein."[199] He has not isolated nor analyzed the so called "bark" yet alleges he can "see that the bark is synthetic, polarized acts as a polypropylene optically, it is a polypropylene. This is the type chemical analysis I do under microscope. I analyze optical properties of the material." One cannot determine a material's chemical composition by viewing its optical properties with a light microscope.

Moreover, I have consistently shown unequivocally, via FTIR spectroscopy analysis, the outer layer or deposit on explanted Prolene is protein, and by Iakovlev's admission, proteins will absorb dye, while Prolene will not.[200]

It is important to pay close attention to the Iakovlev statement "the layer of degraded bark is seen in all polypropylene mesh explants I examine, irrespective of their exposure to vaginal environment or acute inflammation." This statement is further confirmation of the widespread and pervasive use of formaldehyde-protein crosslinked fixation in surgery, and the well-established fact that proteins instantly and efficiently adsorb upon Prolene's surface after its implantation.[201] Moreover, it clearly establishes the presence of the formaldehyde-protein composite polymer on explants. However, Iakovlev's opinions give no attention to, or admission of, the flesh-protein-formaldehyde polymer formed during the fixation process. He completely ignores its presence. Consequently, among Iakovlev's opinions are, the formaldehyde-protein polymer does not exist; and this is patently incorrect. We know his opinions are incorrect given the fact all explants delivered to and evaluated by Iakovlev were fixed in formalin, and the 1949 Fox article on formaldehyde-fixation is very well-known. [202] These facts cannot be disputed. Thus, factors all explants have in common are:

- all are fixed in formaldehyde,
- all contain flesh, all form a formaldehyde-protein polymer or shell around the fiber(s), and
- all are subjected to histologic tissue processing.

This sequence of events and polymer formation, is not recognized, or is ignored, by Iakovlev. Thus he employs a flawed methodology for arriving at his opinions.

The Iakovlev report of July 7, 2014 (page 3) states, "Another example of a specific finding is polypropylene degradation. The degradation material shows changed physical properties-cracking, and chemical products are released during the degradation process."[203,204] However, no reference(s), nor scientific data exists for these erroneous and sweeping statements. The claims lack credibility, are scientifically unfounded, and consequently are unreliable. He has not provided data for any physical property change, no data to confirm which, if any, chemical products are released during the so called "degradation process," and no data to confirm chemical degradation of Prolene.

Iakovlev once again states (page 3) "Most specimens come as formalin fixed tissue …" thus all samples used in Iakovlev's work were fixed in formaldehyde.[205,206]

Iakovlev states (page 5) "degradation bark measured by eyepiece micrometer in filament cross sections closest to a perfect circle." However, he has no proof that his so called "bark" is degradation of any type.[207,208]

Section 1.3 (page 9) speaks to the issue of mesh hardening via gross examination, in part.[209,210] Yet there is no mention that "formaldehyde-protein crosslinking fixation" of the explants to which he referred, significantly influences mesh hardness. Neither does he speak to the issue of fixation, the chemical reactions involved, molecular contraction, nor the hard, brittle shell formed as a fixation process product. Thus, any opinions rendered without due consideration of this well-known chemistry are without proper scientific consideration **or** support.

The statement “Several observational and experimental studies showed that polypropylene used in the mesh degrades while exposed to the body environment” (page 11) is without references or any corroborating scientific proof.[211,212]

The statement “The granules lost the color at the more degraded outer layers (Figure 25a, b, and c)” deserves a response:[213,214] No technical or scientific evidence is provided to support the statement “granules lost color.”

> Response: Iakovlev states the bark originates from “polypropylene itself.” Close examination of 25a, b, and c confirm the angle of observation and the fiber depth of observation must be considered as well as the tenacious adhesion of the protein-formaldehyde fixation product. Moreover, the colorant, CPC or copper phthalocyanine blue is supplied in powder form and dispersed during the extrusion process.[215,216] Thus, attempts to determine degradation based on visual observation of colored powder dispersion is highly suspect and without scientific merit.

The statement “Further proof that the outer layer is a synthetic material was obtained from immunostaining for myeloperoxidase…..” (Page 12 Iakovlev report).[217,218]

> Response: The outer layer, as described by Iakovlev, has been confirmed by plaintiff’s expert and me to be proteins.[219,220] Iakovlev’s statement continues with “Since the bark is brittle (cracking), a calcified material needs to be ruled out. Nearly all hard brittle structures in the human body are hard due to calcium deposition.” However, Iakovlev is discounting the hard and brittle crosslinked protein formaldehyde polymer formed during fixation. The fixation product is well known to be hard and brittle and does not require the presence of calcium to be characterized as such.

Iakovlev’s section 1.4.2.1. (Page 12) titled “Ruling out manufacturing coating and formalin fixation artifacts” is totally without merit.[221,222] Consider the statement, “Samples of unused, new trans-obturator tapes of Ethicon and another manufacturer were subjected to the same formalin fixation, chemical processing, paraffin embedding and staining procedures as diagnostic specimens. The meshes were placed in formalin and samples of mesh were taken at 1 week, 1 month and 4 months. After 4 months of formalin fixation the new mesh showed no stainable layer (Figure 29a, b).

> Response: Of course not, none would be expected given there was no flesh present, and since there was no flesh, no proteins were included in the test. The test did, however, prove that polypropylene does not react with nor accept histological stains. Note the last sentence where Iakovlev speaks of tissue processing, and claims that his test rules out processing as a cause of the “bark”. The experiment and conclusions are without merit given no tissue was present for formalin fixation and there was no opportunity for artifact formation.

Section 1.4.2.2 speaks to the issue of electrocautery effect on bark.[223,224] The surgeon removing the tissue used temperatures exceeding 200°C degrees to cauterize flesh in order to reduce bleeding. However, proteins are tenaciously bonded to Prolene *in vivo* and cauterization

exposes both Prolene and proteins to high temperatures instantaneously. Accordingly, Prolene will melt and flow freely at this temperature (Prolene melting point is app. 162°C). The result would be a composite like structure including both materials; Prolene and the formaldehyde-protein composite. No confirming analytical data such as FTIR spectroscopy was reported as having been performed for these sites, and one absolutely cannot determine chemical composition based on light microscopy. Moreover, the statement "The bark also mixed together with the non-degraded core during melting forming common pools indicating that the core and the bark are of the same original material" is without any scientific foundation.[225,226] It is not a requirement for one to have "the same original materials" to form a "common pool" of melt. The melting process transforms Prolene into a liquid which will encompass adjacent or joining materials and in so doing, form a single mass, both of which may be melted. When Prolene is transformed into a hot flowable liquid by melting, the extent or direction of flow cannot be controlled.

The Iakovlev, Section 1.4.2.3 Relationship between the bark thickness and *in vivo* exposure, makes the statement, "The correlation coefficient was showing a strong association between the bark thickness and the mesh *in vivo* exposure indication its formation while *in vivo*."[227,228]

> Response: It must be remembered that all tissue examined by Dr. Iakovlev was fixed in formaldehyde by others prior to Iakovlev's sample receipt and analysis, and consequently formation of the formaldehyde-protein polymer shell around PP fibers occurred prior to Iakovlev taking possession of the explants. Thus, Dr. Iakovlev once again discounted the known chemical reaction of formaldehyde and protein with this and other statements.

Section 1.4.3 Transmission electron microscopy (TEM) in part confirms my work and my conclusions.[229,230]

> Response: That is, Iakovlev's "bark" is distinctly different from Prolene, it is more porous than Prolene, and it measures in the range of 4 microns. My work has likewise shown the crosslinked polymer of formaldehyde-proteins to be irregular, with multiple cracks, some cracks extending through the full formaldehyde-protein polymer, and either stopped at the Prolene surface or turning parallel to it.

An important, and telling, observation by Iakovlev is that the cracked protein-formaldehyde polymer shell (called "bark" by Iakovlev) did not extend into or through the PP fiber. Consequently, there was no crack propagation into Prolene, and no loss of Prolene mechanical properties would have occurred. Had the so called "bark" been Prolene, the crack would have propagated through the entire fiber resulting in fiber cleavage. Crack propagation is a well-established concept.[231] The fact the cracking material did not propagate into and through Prolene confirms it is not Prolene.

Dr. Iakovlev's opinion of, the "degradation and cracking of PP" with the findings of cells wedged in the cracks, lacks merit. One must consider the explants when removed, placed in formalin, handled by the surgeon, then handled by those who removed them in Dr. Iakovlev's laboratory, and while preparing them for microscopy studies, particularly during the microtoming process.

Given these wet materials are flexible, with a hard, brittle polymeric shell surrounding the fiber, tissue or cells can physically find their way to the cracked protein-formaldehyde polymeric shell during any one of these slide preparation maneuvers. Moreover, flaking of the protein-formaldehyde polymer itself into the "cracked" areas could readily occur. In any event, there are multiple opportunities for the "cracked" areas to be partially filled by fragmented polymeric materials.

Iakovlev makes the statement "The surface defects were filled by extracellular tissue matrix and there were sites of collagen anchoring to the surface (Figure 37)." This explains the adherence of the so-called "bark" to the tissue" yet is omitting one very important concept; i.e. Iakovlev's "degraded bark" is crosslinked formaldehyde-protein fixed tissue, they are one-in-the-same, and formation of strong adhesive and cohesive bonds are expected and known to occur.[232]

> Response: The statement, "Mesh degradation alters polypropylene properties" is completely without merit or supporting scientific data, as is Iakovlev's following statement "The degraded layer has cracks showing its loss of elasticity and hardening."[233,234] Iakovlev follows these two erroneous statements with "As a result, it introduces changes to polypropylene mechanical properties and therefore contributes to mesh deformation and hardening," for which he possesses absolutely no supporting evidence. To the contrary, Dan Burkley's 7 year dog study proved unequivocally physical properties of implanted Prolene improves during implantation, not diminishes. After explanting and testing sutures it was experimentally confirmed that implantation provided significant mechanical property improvements such as toughness and elasticity, with no meaningful loss in molecular weight.[235] Mesh deformation/molecular contracture is well known to be a result of the formaldehyde fixation process, and is accompanied by hardening.[236] Burkley's suture explants were not "fixed" in formalin, and thus the crosslinked formaldehyde-protein polymer formed during the fixation process did not and could not form.

Iakovlev's section "Polypropylene Degradation," page 94 of the Iakovlev July 7, 2014 report states:[237]

> "Polypropylene, as shown, degrades in the human body forming a layer of degraded material resembling a tree bark. The bark retains the blue granules and optical properties of original material, however, it shows porosity/cracks and brittleness, which is not seen in the non-degraded polypropylene. This indicates that degraded polypropylene forms a continuous hardened tube-like sheath with altered physical characteristics."

The prior statement is indicative of all Iakovlev's explant examinations. His statements continue to be without consideration of the well-known and critical, to this issue, chemical reactions of "tissue fixation." All human proteinaceous material will react with formaldehyde (formalin) and the result is forming of a crosslinked polymeric structure.[238] In the present instance, human tissue completely encapsulates explanted Prolene fibers, and consequently the crosslinked formaldehyde-protein polymer formed and surrounded the Prolene fibers. This polymerization process produces a hard, brittle, and insoluble shell surrounding explanted Prolene fibers. It is this reaction that typifies "flesh fixation," and that is its purpose. While the medical community has utilized this process for more than 50 years, its fundamental chemistry is apparently

overlooked, but is central to the understanding of the issue in question. Flesh, bacteria, inflammatory cells, all possess proteins and consequently Prolene's surface is surrounded by proteinaceous materials, all of which possess strong adhesion to Prolene. Thus, it is not unexpected that drying the protein layer, and physical manipulation for its removal, would result in some artifact formation outside the body. This phenomenon has been confirmed and reported.[239]

Dr. Iakovlev has ignored the chemistry of fixation. He has ignored its resulting dramatic transformation of flesh properties. Dr. Iakovlev has mis-assigned formation of the hard, brittle protein-formaldehyde polymer as degraded Prolene. He readily admits Prolene does not receive dye but contends the "bark" or degraded Prolene as he calls it, does take dye and is stained. These are contradictory statements. He makes such assertion without any scientific supporting data. Furthermore, he has not, according to his report, produced degraded Prolene and determined its dye characteristics. Therefore, he has no way to know how degraded Prolene "looks" or "takes dye" any differently than pristine Prolene. Simply put, his methodology is flawed as he has no "scientific control" from which to draw conclusions. Consequently, his assertions are totally subjective and disregards the 60+ year old chemistry of the fixation process, and its effects on explanted Prolene and Prolene examinations.

Iakovlev continues with the following, "Cracking indicates shrinking forces within the bark. Degradation products are released in the tissue and play a role in the continuous inflammatory reaction and additional complications." It is well known within the medical community, and particularly among pathologists, that the "flesh fixation process" causes tissue shrinkage. This well recognized and publicized fact is ignored in the Iakovlev report.[240] It is interesting that Iakovlev, a pathologist, is apparently unaware of this process and its effects.

Moreover, Iakovlev's statement "degradation products are released in the tissue…," is without any scientific data and should be disregarded. See page 302, March 18, 2014 Iakovlev deposition wherein the following question and answers were proffered:[241]

> Q: The crack can be from the body's proteins, that's one source?
>
> A: Yes
>
> Q: And another source for your opinion is that the cracks can be from degraded polypropylene?
>
> A: Yes. So if you see cracked material in the surface, it can be either polypropylene crack or protein.
>
> Q: Did you attempt to isolate this bark that you opine is in the slides and chemically analyze it?
>
> A: No

Furthermore, in a series of questions regarding proposed degradation and the hypothesis for degradation, the following dialogue occurred (page 306)[242]

> Q. There's people who analyzed whether there is alleged oxidation, and they found that there is no oxidation. You're aware of that research, correct?
>
> A: I don't know. This is polypropylene, it's completely different, behaving differently than non-degraded polypropylene. And it doesn't form by formalin alone, it forms *in-vivo.*

The statement "it forms *in-vivo"* is sheer speculation as he has absolutely no way to know that formation of the "bark" occurs *in-vivo,* given he first receives the explants after they have been "fixed" in formalin.

To further confirm Iakovlev's flawed attempts to establish Prolene degradation via staining and microscopic examinations, consider his trial testimony of November 6, 2014 (Amal Eghnayem vs. Boston Scientific). His testimony on page 95 reads (lines 3-5) as:[243]

> A: "Chronic foreign body inflammation is mainly microphages. You can see dots. These are blue dots of the nuclei of microphages." That being said, consider his statement of page 100, lines 10-12; "And the background clear material is clear polypropylene. The blue dots within it are the blue granules which are added to color it."

Given he has no analytical data to confirm chemical composition of the "blue dots" and his identification of two very dissimilar materials as "blue dots," one macrophages and the other polypropylene, it is clear Iakovlev's opinions lack scientific standing and to say the least, are misleading, confusing, and simply wrong.

Iakovlev continues his unsupported testimony in the matter of Maria Cardenas on August 18, 2014, page 581 beginning at line 7.[244] Iakovlev testifies, "In this case, the long chains of polypropylene are broken down, and there are microcavities in it. Then the next step for me was to see if this – this layer is, in fact, polypropylene, and I examined it in polarized light. We use polarized light in pathology to identify foreign bodies." He continues on line 20 with, "In this case, polypropylene polarizes light, we can see it, and the bark which is peeling off is also bright. So this finding indicates that the bark is, in fact, polypropylene."

> Response: I have established within this report, with scientific references, that proteins are also birefringent in polarized light and consequently polarized light cannot be used to distinguish the presence of only polypropylene in the presence of proteins, as proteins are likewise birefringent and polarize light. Iakovlev continues testimony on pages 583 (line 23) and 584 (lines 1-3) respectively, with statements, "Then I can examine the same sections in polarized light, and polypropylene becomes bright, you can see it, both the degraded part and non-degraded part." "All foreign material is bright." A protein-formalin composite structure is a foreign body, yet Iakovlev gives absolutely no consideration to its presence.

It is scientifically invalid to make sweeping statements without supporting scientific evidence. Consider for instance, page 126 of the Nov. 6, 2014 trial testimony:[245]

> Q: (line 5-7) Doctor, can you cite to any literature that you rely upon for the appropriateness of using polarized light to evaluate potential degradation of a polymer?

> A: (lines 13-15) In terms of polymer, I don't know. In terms of polypropylene and histological sections, no. My publications were the first publications.

Dr. Iakovlev's statements amount to an unsupported theory that raises more questions than provides answers. Consequently, Iakovlev's writings hold no scientific merit, and by his words are scientifically unsupported. Iakovlev is completely unaware of, or chooses to ignore, the formation of the fixative crosslinked formaldehyde-protein polymer, and that proteins are polymers.[246] Iakovlev has leaped to a conclusion and mischaracterized the crosslinked protein-formaldehyde polymer shell as Prolene; a fundamental flaw in his conclusions. Iakovlev's theory that the outer dyed layer is degraded Prolene, does not account for the obvious "protein fixation" product. It also does not account for his own writings that Prolene does not accept histological dyes. It is obvious Iakovlev's "bark" is the dye accepting outer, porous layer of the crosslinked formaldehyde-protein polymer shell. It is well known, and Iakovlev agrees, proteins accept dyes while polypropylene does not. It is my belief that Dr. Iakovlev's opinions regarding degradation of Prolene in the human body are erroneous, unsupported, incomplete, and scientifically unfounded.

Iakovlev states in his July 7, 2014 report (page 4) "To understand the related pathological processes and make a correct diagnosis, pathologist need to understand the function of the devices being analyzed, their physical characteristics, surgical and other techniques introducing the objects into the body." He goes on to state, "I possess this knowledge and expertise and these routine methods were used for assessment of explanted meshes." However, when reading this same report it became very clear that he does not appreciate or understand the full implication of the "routine methods (he) used for assessment of explanted meshes."[247] Those "routine" methods involved mesh fixation and its concomitant effects, all of which were totally disregarded by Iakovlev and are readily available in the open literature. For example, consider the writings of Dr. Susan Lester, a Harvard pathologist, in the **Manual of Surgical Pathology** with respect to this issue. Dr. Lester's credentials include Assistant Professor of Pathology Harvard Medical School, and Director, Breast Pathology Services, Brigham and Women's Hospital Boston, Massachusetts.[248]

Dr. Iakovlev's October 6, 2014 Report regarding the Patient 3 matter is little different from his prior reports I have discussed above. His opinions and conclusions expressed in the Patient 3 report suffer from the same problems as explained above.[249]

Response to Iakovlev's April 24, 2015 Report

In the April 24, 2015 Expert Report Iakovlev once again speaks to the issue of polypropylene degradation although he readily admits he is not a material scientist.[250] His selection of references, ostensibly to support his thesis, does not, in fact, do so. For instance, (page 9) he writes "Liebert, et al found "polypropylene will degrade *in vivo* over time if not adequately protected by antioxidants." However, he chooses to omit that Ethicon's Prolene is not just polypropylene, it is formulated polypropylene with added ingredients, two of which are effective polypropylene stabilizers. Liebert's article states emphatically "Infrared spectra and mechanical testing of implanted and non-implanted filaments containing an antioxidant show no change in chemical or physical properties as a result of implantation."

I have previously responded, in this report, to Iakovlev's apparent adoption of data and hypotheses of Celine Mary, Costello, Clavé and Wood on the matter of Prolene degradation.

The Iakovlev statement (page 10, April 24, 2015) "Environmental stress cracking and/or oxidative degradation facilitated by macrophages have been found to be the most likely mechanisms to explain polypropylene's *in vivo* degradative processes" has no basis in fact. The statement is followed by 16 references, none of which possess any quantifiable data substantiating/confirming Iakovlev's stated opinion on Prolene degradation by ESC. I have responded to ESC as it relates to polypropylene earlier in this report (page 21-22)

That Iakovlev likens the environmental conditions of Prolene explants and their *in vivo* response to that of an exterior environmental exposure (April 24, 2015 report) confirms his lack of understanding of material properties, and their relation to use environment (see Iakovlev references 448 and 467). The former report is on the effects of polypropylene in artificial and sunlight exposure while the latter relates to *in vivo* conditions. Prolene implants are not exposed to ultraviolet light *in vivo,* with the exception of ophthalmological sutures. It is important that the latter, Sternschuss, *et al*., manuscript is a review of a myriad of articles and espouses the authors opinions. They performed no independent laboratory work and data therefrom. Numerous statements therein are without sound scientific data. As an example, consider the following:

- "Generally we have no idea of exactly what was used in a particular mesh construct." Yet they are freely opining on the properties of Prolene and its material composition.
- "After implantation PP mesh absorbs certain substances from bodily fluids, notably cholesterol and fatty acids, which could alter the physical and mechanical properties of the mesh." They are right, yet apparently do not understand why. Their implication is that absorbed materials will adversely affect physical properties, yet Burkley's 7 year dog study proved otherwise. His data showed overall improvements in physical properties such as elongation and toughness. These property enhancements can be ascribed to well-known plasticizing and toughening effects of fatty type materials found *in vivo.*[251,252]
- Finally, the Sternschuss, *et al.* manuscript was poorly written and data documented that it elicited a lengthy letter to the editor. The following rebuttal quote describes this article in generalities very well, i.e. "We believe this article is biased and contains multiple statements that are poorly supported by quality science" and "statements with partial truth include results from the article by Clavé et al taken out of context." For example, the authors emphasize oxidation during processing and then after implantation. However, Clavé made statements their analysis was unable to confirm oxidative damage of implanted mesh leading to degradation. This very important statement was omitted by Sternschuss and co-workers.[253] The Letter to the Editor is critical of the author's reliance on Clavé's writings noting finally that "Clavé could perform chemical analysis on only 32 of 84 explants, which is too small a sample for an appropriately powered study." Moreover, the title of the Clavé, *et al*. study "Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants" is very misleading.

Iakovlev continues his so-called degradation discussion (page 10) and states, "Ethicon's internal documents, was used by Ethicon's scientists-along with histological methods-to

characterize the physical properties of explanted Prolene sutures which, as discussed in detail below, lead Ethicon's scientists to conclude that the cracking observed on the surface of Prolene is the polypropylene and not proteinaceous." However, this mis-states the facts of the Ethicon documents. For instance, ETH.MESH-15955438 describes B. Matlaga experiments of March 23, 1983 wherein Prolene explants ranging in *in-vivo* residence times from 2.5 to 7.0 years, and fixed in formalin, were examined by light microscopy and polarized light. It was noted that 3 of 5 explant samples showed no cracking. It is important to note that no mention was made if the samples were dry or wet when examined, but all were fixed in formalin. Ethicon documents of March 29, 1983 (ETH.MESH 1595544 thru 15955440-15955442) continued with examination of Prolene sutures used to secure a Dacron graft. The formalin fixed Prolene sutures were not cleaned in any way and thus necessarily contained adhered, formalin-fixed flesh. The Histological Evaluation (page ETH.MESH 15955442) stated "No endothelial cells were present on what was judged to be the luminal surface. Only one cross sectional profile of PROLENE was contained in this slide. No evidence of cracking was noted." One sample only was available for testing of tensile strength and gave 54% of its pristine value; however, at least 5 tests are required for statistical validity and damage of the suture could not be explained.[254] Moreover, no strain or elongation test data was collected thereby not allowing suture toughness to be determined.

On March 25, 1983 Emil Borysko, an Ethicon scientist, provided data on "sutures explanted after 2 to 6 years implantation (ETH.MESH 15955453-15955454)." Nine samples were submitted for evaluation, three were stored in formalin from their time of explanation, and the remainder had been allowed to dry. The uncleaned samples were examined microscopically. In essence, the results confirm most of the dry samples showed some cracking and the wet samples were essentially free of cracks. The wet samples were allowed to dry, and then examined. The General Observations and Conclusions of this report are as follows:

- Sutures kept in the wet state do not exhibit cracks
- Upon drying, cracks appear-this was actually observed happening by drying "83-165 6 yr. wet on the microscope stage."
- The work of Dr. Peter Moy is further support for the work of Dr. Borysko (see ETH.MESH 00006325) wherein wet explants, even though fixed in formalin, are far less likely to crack than dry explants.

It is puzzling that Iakovlev would reference the 1984 Ethicon Matlaga report (ETH.MESH 15955462-15955468) as part of his "degradation" theory as she describes the following:

- Six formalin fixed tissue samples of Prolene sutures were evaluated without cleaning
- Sutures were kept wet and examined by light microscopy while wet and dry
- Samples 1-5 showed no surface cracking in light microscopy examinations (ETH.MESH 15955462) as sutures or histological sections.
- Sample 6, a 7 year explant, showed surface cracking
- The average breaking strength (tensile strength) for the size 3-0 Prolene was 76.5%, and for size 4-0 was 98.25%-elongation data were not collected.
- Only one sample was available for the 5-0, 7 year suture explant which showed 76% tensile strength retention.

Finally, even though the author notes "This breaking strength data must be viewed with caution since damage to strands during removal may have occurred despite efforts to prevent it," the tensile data of uncleaned samples, are quite good given the authors admonition. Once again, the data confirms, a simple but important concept, dry tissue is highly susceptible to cracking and plays no role in Prolene degradation.

The April 25, 2014 Iakovlev report continues to defy scientific and chemical principles by stating "Recently, degradation of polypropylene was detected using histological and transmission electron-microscopy approaches." One cannot confirm chemical composition and changes in chemical species and composition with dyes and microscopy as per Iakovlev. For instance, Iakovlev essentially defines degradation as "cracking" of the polypropylene surface, yet he has no scientifically valid means of identifying and confirming the chemical composition of polypropylene.

For instance, consider Iakovlev's beliefs:

- Polypropylene **does not** stain with H & E dyes. Polypropylene is birefringent
- Polypropylene responds to polarized light because it is birefringent
  With this said, consider what else Iakovlev testifies to:
- Collagen (proteins) **will stain** and polypropylene will not
- Collagen (proteins) are birefringent as is polypropylene
- Collagen (proteins), because it is birefringent, responds to Polarized light, as does polypropylene because it is also birefringent

With respect to birefringence and polarized light response, both Collagen and Polypropylene respond affirmatively. There are many birefringent compounds with varying chemical structure and composition that respond to polarize light.

However, while collagen and polypropylene both respond to polarized light, only collagen will stain, while Polypropylene will NOT stain; the perfect example of two very different chemical species but both being birefringent. Consequently, in the absence of FTIR spectroscopy or other chemical structure identifying tools one can only conclude that two materials, one accepting dyes, and one not accepting dyes are **different** in chemical composition; and they are. It is only with FTIR and other analytical tools can one specify the chemical make-up or structure of the two different compounds. My work with FTIR spectroscopy has made this determination and the composition of Iakovlev's "bark" has been confirmed as proteins, not Prolene or even degraded Prolene.

It is puzzling in the face of his beliefs Iakovlev writes the following in the International Journal of Medical, Health, Biomedical and Pharmaceutical Engineering, Vo. 8, No. 9, 2014. "A stand-alone finding was the detection of polypropylene degradation. The filaments in all (100%) of both lightweight and heavyweight designs showed a layer of homogeneous material surrounding the filaments. The material stained purple by H&E stain which was different from the clear filament core. To test if the material is synthetic the sections were examined in polarized light. Both the core and outer layer showed the same optical properties in polarized light. These findings indicated that the layer is degraded polypropylene. The degradation layer

resembled a tree bark: it surrounded the filaments and showed cracking and partial detachment from the core." However, Iakovlev has stated repeatedly that polypropylene cannot be stained by H&E dyes and proteins do accept H&E dyes. Iakovlev's "bark" accepts H&E dyes and therefore simply cannot be polypropylene as he states in the referenced and published manuscript.

Iakovlev, with co-authors S. Guelcher and R. Bendavid published in "OFP-13 Joint Oral Free Paper Session IT in Pathology/other Topics, a writing titled, "*In Vivo* degradation of surgical polypropylene meshes: A finding overlooked for decades." Excerpts from the paper follows: "The degraded polymer formed a demarcated layer at the surface of the filaments similarly to a tree bark. The bark traps histological dyes due to its porosity and is easily visible by conventional microscopy. A number of findings confirmed that the bark originates from polypropylene itself and forms *in-vivo*. Conclusion: An easily visible by conventional microscopy, the finding has been passing unrecognized through pathologists' microscopes for decades."

- Once again he writes for the scientific community that "bark traps histological dyes due to its porosity," when he has repeatedly testified that polypropylene does not accept dyes. Moreover, well established scientific facts state clearly that staining can only occur as a result of a chemical reaction between a dye and, in this case, flesh.

- Consider the following:

  H & E dyes must react chemically with a material before the material will stain appropriately.

  The following information is taken from the "Chemistry of H & E Staining," published in *The American Journal of Medical Technology*, Vol. 40, Number 11, November 1974. "Many individuals with long experience in histology still do not completely understand the Chemistry of H & E Staining." Consider also, the writings of M. Lamar Jones, who published "Mastering the Trichrome Stain" in *Connection 2010*.[255] The article speaks of methods of staining, i.e. "At the onset it must be made clear that the methods control how ionized acid dyes react with the ionized basic tissues. This is the fundamental principle on which they depend and the explanation is only about how that fundamental reaction can be manipulated." "The components involved in histological staining are dyes and proteins. The fundamental process involved is the chemical bonding between the carboxyl groups of the one and the amino groups of the other."[256] "pH Control-Staining depends largely on the attachment of dyes to proteins. These have both positively and negatively charged groups."[257] Successful histological staining is all in the chemistry and not porosity as alleged by Iakovlev.

  Lester's Manual of Surgical Pathology describes the proper method of slide staining.[258] There are several steps for washing and blotting slides during the staining process in order to remove gross or unused stain. In none of the staining steps is substrate porosity mentioned, but proper sample pH to affect the chemical reaction is a central theme of the process. Warnings are made, i.e. "slides are left in xylene until over-slipped to avoid

drying artifact that can make interpretation difficult or impossible." Given artifacts are typically defined as the unwanted effects of a process, fixation artifacts are "largely restricted to a few items such as deposits from the fixative or its reactions with tissue components, and the physical effects of fixation we would prefer to do without, such as detectable shrinkage, both at the gross and microscopic levels, the hardening of some tissues which causes chatters parallel to the knife edge; and the brittleness from some fixatives which results in shattering and cracking during sectioning."[259] This phenomenon is easily recognized in Iakovlev's Fig. JR-16a where it is obvious the approximate right one-half shows loss of adhesion between Prolene and collagen thereby offering the viewer a "side" view or an angle of observation. In contrast the approximate left one-half shows strong adhesion of collagen to Prolene and also loss of collagen cohesion thereby opening a void between collagen molecules. Consider also Fig. JR16B which is stated to be the same field as in 16a but under polarized light. This is a classic example of three birefringent materials and all appear with different color intensities and hues. Consider for instance, the central portion of the photomicrograph is known to be Prolene, and Prolene is known to be birefringent. The central layer of the photomicrograph is collagen and collagen is known to be birefringent, and finally consider the outermost portion of the photomicrograph said to be collagen, again birefringent. One must also consider the angle of observation for each segment of Fig. JR16B supporting birefringence for all. Since both collagen and Prolene are birefringent you cannot use polarization alone to make a chemical distinction between the two materials.

Figure JR17a is an excellent example of artifact construction showing clearly shattering of the collagen layer presumably during microtoming. In viewing the blue portion of the photomicrograph, labelled non-degraded core by Iakovlev, the viewer transitions to the ruptured collagen layer separated by paraffin (white area). This photomicrograph is an excellent example confirming tenacious adhesion of collagen to Prolene, and cohesive failure of collagen alone. This photomicrograph depicts an H&E stained sample wherein, and by Iakovlev's testimony, collagen stains pink, as is the case in Fig. JR17a. There is no degraded area; rather this photomicrograph depicts loss of cohesion of collagen and strong adhesion of collagen to Prolene.

Fig. JR 18b, identified by Iakovlev as being the same field as JR 18a, but under polarized light is stated by Iakovlev as an example of an artifact, i.e. via his statement, "In this field the non-degraded filament core detached from the slide during processing."

This clearly represents an ideal example of artifacts generated during the staining process.

- He further states "a number of findings confirmed that the bark originates from polypropylene itself and forms *in-vivo*," yet he offers no such findings.

I have also reviewed Iakovlev's March 5, 2015 testimony in the Bellew litigation and the following responses are helpful to fully and completely understand Iakovlev does not understand the chemistry of staining or chooses to ignore it.[260]

> Mr. Anderson, Question: What is the significance of that cracked outer layer that we're seeing in 1910-G?
> Answer: This is the bark layer or outer layer of the degraded polypropylene. It's the same wood but because it was exposed to the outside environment, it's all cracked. It has all these crevices, cracks, and cavities. The same thing happens with the polypropylene. When it's exposed to the body environment, it cracks and forms these cavities, and the histological dye, it gets trapped in it so it sticks in between. It's like clothing. The dye gets in between the fibers in the clothing and that's why it stains. The non-degraded polypropylene is solid, so it cannot be stained."[261]

When cross examined by Mr. Thomas why polypropylene was not stained by H&E dyes, he again answered that "polypropylene is solid, so it doesn't have cavities to trap dyes." When asked if "Isn't it true that typically an H&E stain, hematoxylin and eosin stain leaves their colors by a chemical reaction?" he responded "Not exactly chemical reaction. Most of the dyes are trapped... So, it's not fully chemical reaction when molecules form new molecules. It's more of a trapping or binding of the dye molecule inside the material." Thus, given his statements, it is absolute that Iakovlev does not understand the chemistry of staining yet his entire theses of degradation is based on an incorrect assumption that "degraded Prolene" stains. However, MacLean has proven experimentally that degraded Prolene does not stain.[262]

His testimony that (1) he does not know if polypropylene possesses a charge or not, and (2) admission he does not know if the reason polypropylene does not accept dyes is due to the fact polypropylene is not charged,[263] again is absolute confirmation of his lack of knowledge of the staining process for which he has and continues to make invalid and unsupported statements regarding Polypropylene's properties.

He provides an analysis of his exhibit P-1910G in part by the printed designations on the photomicrograph. It is instructive that Iakovlev has testified the clear areas of such slides are wax where there is no flesh or Prolene. Other sections of the H&E stained slide are pink to blue-purple; a portion of which Iakovlev labels as Collagen. However, Iakovlev also has labelled a portion of the slide as "Degradation bark," and this so-labelled "degradation bark" is stained pink-blue-purple, precisely the colors one would expect of proteins. It must be remembered that Prolene will not accept dyes, and proteins will readily accept dyes, therefore Iakovlev's dye accepting "degradation bark" as labelled cannot be of Prolene origin, but rather from proteins.

Furthermore, P-1910M is an excellent example of the type effects light manipulations can produce. For instance, Collagen, wax and a portion of Prolene all show identical polarization effects by completely blocking the light path.

Iakovlev fails to testify about P-1910-O, a trichrome stain photomicrograph. This photomicrograph confirms adhesion of Collagen and other proteins to Prolene therefore defeating the idea of "degradation bark." For instance, Iakovlev has testified the green color represents Collagen, and it is known that cytoplasm, fibrin or muscle are pink-red.[264] The photomicrograph confirms adhesion of a stained and formalin-crosslinked protein coating to Prolene, and is not degraded Prolene.

Photomicrograph P-1910-U speaks to the absence of calcium in tissue but as importantly to the consistent staining and identical color of Collagen and the protein layer, i.e. the protein-formaldehyde coating.

I have also reviewed the Iakovlev report of May 22, 2015
RE: Mr. Donald Iholts, hernia mesh excision

Much of the report is included in other Iakovlev documents I have read. Therefore, my comments will focus on specific issues of interest as related to his past testimonies and new comments included in the May 15, 2015 report.

Iakovlev continues to emphasize Environmental Stress Cracking and identifies it as the most likely mechanism for his proposed polypropylene's degradation by his page 8 statement, i.e. "Environmental stress cracking and/or oxidative degradation facilitated by macrophages have been found to be the most likely mechanism to explain polypropylene's *in vivo* degradation processes."[265] However, the multiple sources in scientific literature explicitly refute this tenet.[266,267,268,269,270] Moreover, he continues to cite references not germane to the present instance; see his reference 448 dealing with artificial light and sunlight exposure of polypropylene.[271]

Iakovlev continues to stress the supposed importance of cracks and cavities to the staining process (Figure Set 12a) and ignores artifact creation and the chemistry of H&E and Trichrome staining.[272] Figures Set 12a confirms both Hematoxylin and Eosin have exerted their color producing stain of the protein-formaldehyde composite shell surrounding the Prolene fiber. Iakovlev continues to ignore his own admonition that PP cannot accept H&E stains.

Figure set 13a[273] is an excellent example of the interface of Prolene and the adsorbed protein coating wherein Iakovlev's arrows confirm excellent adhesion of proteins to Prolene as seen through an angled view, thereby allowing dye particles of Prolene to be seen through a thin protein layer. Figure Set 14a of trichrome staining confirms the presence of protein/collagen (light green) and cytoplasm, fibrin and muscle (red).

Figure Set 17 of Von Kossa calcium stain is instructive in its tissue staining consistency and artifact formation (cohesive failure of tissue).[274]

Iakovlev presents Figure set 22 wherein he states "Mesh filaments show cracking immediately after excision, before the mesh is placed in formalin or before the tissue is allowed to dry."[275] However, on close examination Figure set 22 is described as "Freshly excised TVT sling after 9 years in the body, washed in saline and tissue-free filaments at the mesh edges are photographed immediately after excision (no contact with formalin and no drying), regular light microscope, 20x objective, cropped image." One knowledgeable in the discipline must ask "how can the filament be tissue free if it has not been cleaned in any way?" In my opinion it cannot as it is well-known that protein coatings form immediately with fiber/mesh implantation to form a tenacious bond between the hydrophobic Prolene and collagen.[276] Therefore, tissue must be present given no cleaning was performed before microscopic examination. The topic of tissue

cleaning, and fixation has been discussed extensively by me in this report and will not be repeated.

Iakovlev's Figure D119a is an excellent example of artifact formation, and mis-assignment of H&E stained collagen which Iakovlev has labelled "degraded polypropylene."[277] His so called "degraded polypropylene" stained blue in regular light, while it is well established that polypropylene cannot and does not accept dyes given its non-polar chemical structure. It is also well known that collagen (proteins) readily accept H&E stains, as they have in Figure D119a. Also note the artifact formation with cohesive losses of collagen. Figure D120a is yet another example of extensive artifact formation confirmed by collagen cohesive failures and rupture of the collagen-formaldehyde composite.

Iakovlev's Figures D121a and D122a of Trichrome stain are yet other instructive and helpful photomicrographs. Note the arrows of both point to Iakovlev assigned "degraded polypropylene."[278] Note too that in each, the stain colors are red and green and Iakovlev assigns these as "degraded propylene." Iakovlev assignments are inconsistent with published works who state that "Cytoplasm, fibrin, and muscle stain RED, while Collagen stains BLUE or GREEN. Jones also writes that "At the onset it must be made clear that the methods control how ionized acid dyes react with the ionized basic tissues. This is a fundamental principle of which they depend and the explanation is only about how that fundamental reaction can be manipulated." The article continues with "When the protein component of a tissue is exposed to a fixative agent an interaction between the protein chains and the fixative occurs. Usually a 3 dimensional, insoluble protein "network" is formed." Given the fundamental principle of trichrome staining, is "how ionized acid dyes react with the ionized basic tissues" polypropylene cannot react with trichrome stain. Polypropylene has no acid or basic components and thus no pH. Given these irrefutable scientific facts, Iakovlev's assignments of degraded polypropylene are in error.

I have reviewed Iakovlev's Richard Schmidt report dated March 9, 2015[279] and have the following comments:

Much of this report is identical to others Iakovlev has written. Thus, there will be some redundancy herein.

Figure Set 12a. is titled "Degradation layer (bark) has microcracks and microcavities which retain histological dyes (regular light upper panel), however has the same optical properties (birefringence, bright in polarized light, lower panel) as the non-degraded core, H&E, 100x objective with oil immersion."[280]

Once again it is clear that Iakovlev clearly does not understand the chemistry of histological dyes from which he is drawing sweeping and erroneous conclusions. Consider Iakovlev's continuing statements on microcracks and microcavities; these are in large measure unimportant and do not control the dyeing process. While cracks and cavities allow dyes to wet or come in contact with more surface area than a non-porous media, the dyeing process is clearly one of a chemical reaction between the H & E dyes and proteins, nucleic acids, cytoplasm, collagen and a variety of proteins. When the chemical reaction occurs, the dye is

chemically bound to the tissue it stains and cannot be washed away in the subsequent slide washing step of the histological staining process. Washing is used in the staining process to wash away excess dye(s) that did not chemically react with human tissue. Neither Prolene nor PP will react with H&E dyes. Therefore, PP does not and cannot be changed in color by H&E dyes. Thus, any material that is dyed or accepts color during the staining process must originate from human flesh. This is seen in many, many occasions of Iakovlev's work. Consider, for example, Figure Set 12a;[281] it is well known that Eosin reacts with positively charged species and in the process produced a pink-red color. We see that in the upper-right slide where the pink color is labelled collagen. Intermingled within the collagen is the blue-violet color of Hematoxylin dye (H), and the area Iakovlev has labelled as degraded bark. However, this is a mis-assignment in that PP cannot accept dyes, and thus cannot be colored. The proper assignment is that the Hematoxylin dye has reacted with proteins (collagen + formalin in this case) and in the process the well-known blue-violet of Hematoxylin dye is formed. Notice Iakovlev assignment of the so called, non-degraded core, which is NOT stained. It is PP and PP cannot be stained by H&E dyes. Therefore, the mere fact that the "Iakovlev labelled degraded polypropylene" stains blue is absolute proof his assignment is incorrect. Thus, his conclusions and opinions are not based on well-known chemical principles of H&E dyes are therefore, in error.[282] In Figure Set 12b Iakovlev shows a histological slide wherein the filament core is detached from the surrounding tissue and is not present.[283] The very next Figure Set 13a however, shows the filament core and the detached surrounding flesh. Note the H&E stains of violet and pink confirming presence of proteins and DNA/RNA. It is clear in both the two photomicrographs that the angle of observation of the slide allows one to observe the cut surfaces of flesh and PP filament to be in different essentially parallel planes. In other words, the surface of the PP filament fiber disc is above the surface of the surrounding adsorbed protein layer. Consequently, a side view of the PP disc is in view and one can readily see the blue granular pigment of Prolene.

In Figure Set 13b[284] there is yet another mis-assignment as Iakovlev again speaks of a degradation area but it is well known, and admitted by Iakovlev, that PP does not stain. Thus, if PP does not stain, how can his assignment of degraded PP be seriously considered. It is well known that formalin and collagen (proteins) form hard, brittle surfaces and since their makeup is of proteins, they do accept dyes and color.

Iakovlev's Figure Set 14a of Trichrome stain once again clearly delineates his concept of staining relies on porosity/microcavities and not the chemistry of dyes and proteins.[285] From a very simplistic perspective, how can one possibly rely on a physical phenomenon of porosity to identify the chemical composition of a material?

Iakovlev's Figure Set 14b of a Trichrome stained slide labels green and pink colored materials as "degraded polypropylene" when it has been shown and he has written that PP does not accept dyes.[286] Moreover, the chemistry of Trichrome stains clearly states the Trichrome process stains cytoplasm, fibrin and muscle RED and collagen GREEN.[287]

Iakovlev's Figure Set 17 for Von Kossa Calcium Stain readily affirms the precepts I have set forth.[288] For instance, all the stained materials are shades of pink-red. Likewise, it is clear the area where the two black arrows are pointed is a very good example of flesh in contact with the

filament being essentially identical to all other segments of the slides flesh. In other words, there is no difference in the stained tissue in contact with the PP filament and that within the body of the slide and away from the tissue-filament juncture.

Iakovlev's Figure Set 18 confirms what one would expect. For instance, when PP is immersed in formalin no chemical reaction occurs given no proteins (flesh) are present.[289] However, what will occur is extraction of antioxidants and UV absorbers by formaldehyde.

Figure Set 19a reaffirms Iakovlev's self-contradiction; For instance, he states, "Note that the degradation layer (bark) lost its ability to retain dye after melting. It melted together with the non-degraded core."[290] PP is a thermoplastic polymeric material that can be melted repeatedly without damage to the polymer itself. Thus, the original and non-melted PP fiber will not accept a stain and be dyed and neither will PP that has been melted. Consequently, if it did not retain dye after melting, it would not retain dye before melting; and, we know that to be true. Iakovlev's contention that the so called "degradation bark" lost its ability to retain dyes after melting once again confirms his lack of understanding of PP and of the histological dyeing process, and his gross error in writing and publishing "degradation bark" is PP.

Iakovlev's Figure Set 20a[291] dealing with Transmission Electron Microscopy of "A Specimen of Explanted transvaginal mesh" will not be discussed herein given my uncertainty of the mesh manufacturer.

Iakovlev's section for Richard Schmidt on Polypropylene Degradation should be dismissed for lack of credible data and expertise from which to draw material science conclusions. He has readily admitted he is not a "Material Scientist" yet he continues to opine on Material Science issues, with no credible data.

Iakovlev's Figure RS-24a is yet another example of artifact formation and again mis-assignment of a "degradation layer" as PP.[292] Iakovlev has once again identified Hematoxylin and Eosin stained tissue as degraded polypropylene

I have further reviewed the May 23, 2015 Expert Report of Dr. Vladimir Iakovlev re: Paula Carole Clowe and have the following observations.

Dr. Iakovlev's writings leading up to the examination of Histological images are essentially in keeping with other reports he has written. However, his FIGURES of histological slides are of interest and I will respond to some of his finding particularly when he refers to Prolene degradation. Figure 7a, page 31, clearly shows artifacts of slide preparation with tissue separation. Note the H&E stained bio-film layer attached to and surrounding the Prolene filament. One must remember that H&E stains will not stain PP but will stain collagen and other proteins, as we see in slide 7a, yet both collagen and Prolene are birefringent. The polarized photomicrographs show two most important features of polarization; i.e. slight polarization of the protein layer as it contains Collagen, a birefringent material that polarizes light as is seen, and the varied colors of Prolene and the protein layer showing the effects of light impingement during the polarization process. Iakovlev is in error characterizing the protein coating layer as degraded polypropylene.

He continues his mis-assignment on page 32, Figure 7b. The H&E photomicrographs (top) show blue-pink stained material (remember, Collagen and proteins) which cannot be Prolene given it is non-stainable by H&E dyes. The polarization photos (below) are consistent with this tenet given collagen (protein) is birefringent and polarizes light. It appears the collagen, and remainder of the slide, is in a different vertical plane.

The photomicrographs on page 33, Figure 7c are perfect examples of mis-assignments. It is questionable whether the two top photomicrographs are at the same magnification (100) and the two bottom ones. The top ones are examples of Prolene and strongly adhered collagen-proteins. Remember, proteins are colored by H&E dyes and Prolene is not. Thus, it is clear that the assignment given is incorrect. The higher bottom view at a higher magnification is much easier to confirm tenaciously adhered protein coating to Prolene. The “adhesion line” between the proteins and Prolene is very “tight” and void of any loss of adhesion. Note that Iakovlev himself has assigned the red portion as tissue and blue portion as non-degraded core. However, I am puzzled by and with his mis-assignment of the tissue-Prolene interface as degraded Polypropylene? The photomicrograph represents an excellent example of an almost “picture perfect” adhesion interface.

Figure PC9 is an example of Prolene and the remaining slide portion existing on separate planes.

Figure PC14a is an excellent example of artifact formation during histological slide preparation. For instance, note the separation of collagen layers (cohesive failure) confirmed by wax separation, and the interface of collagen and the protein coating layer (adhesive failure). The right lower portion of the photomicrographs confirm beyond any doubt that the protein coating layer was intimately bonded prior to artifact formation. Close examination of Figure PC14b (polarized light) confirms the protein coating layer and the intact adhesive bond (lower right) as in “regular” light.

Figure PC15 shows both “regular (left) and polarized (right)” light. One can easily confirm a protein coating layer interface in regular light due to H&E staining.

PC-16a, 16b, 17a are examples of protein adhesion to the Prolene interface with some influence of the slide making process. Note the protein coating layer-Prolene interface has been stressed and consequently has weakened the interface. This is supported by Figure PC18a where trichrome stain was used in regular and polarized light. The Trichrome staining process stains Collagen green, and cytoplasm, fibrin, and muscle RED; exactly as depicted in PC18a. Given these color designations, artifacts formed whereby we can see cohesive failure of collagen (green) but excellent adhesion of collagen and the remaining protein coating layer composition of cytoplasm, and/or fibrin and/or muscle (all of which make up the protein coating layer composition). This photomicrograph is an excellent example of how slide preparation can dramatically affect tissue and its orientation. It is also an excellent example of the fact that Prolene does not undergo scientifically significant degradation *in vivo.* It further confirms that those promulgating Prolene degradation *in vivo* simply do not understand or wish to ignore basic facts of chemistry and the staining process. The polarized sample (Figure PC18b) is an

excellent explanation and example of how polarized light is limited in value when examining explants. For instance, the “regular” light photomicrographs on page 76 absolutely confirm the presence of a protein coating layer and the adhesive tenacity of collagen to cytoplasm, fibrin, and or muscle. However, Dr. Iakovlev has identified a protein coating layer in regular light as the “degraded layer” in Polarized light (PC18b). These two tenets are contradictory, hold no scientific merit, and should be disregarded.

Similar errors are made by Iakovlev with respect to Figure PC-19a (regular light) and -19B (polarized light). Iakovlev continues to ignore the chemistry of staining for nanocavities and porosity; totally disregarding the chemical reactions that must be affected between the stains and acid or basic materials.

In summary, Dr. Iakovlev is simply missing or chooses to ignore the fundamental chemistry that control dye staining. The chemistry of dye stains has been discussed earlier and in detail in this report and will not be repeated at this point. Therefore, Dr. Iakovlev’s opinions regarding Prolene degradation are simply wrong; I have seen no compelling scientific evidence that Prolene meaningfully degrades *in vivo,* and my opinion is that it does not. There is compelling evidence to support that tenet, and that evidence has been included and discussed in this report.

I have reviewed the July 2015 paper entitled ‘Degradation of polypropylene *in vivo*: A microscopic analysis of meshes explanted from patients’.[293] This paper purports to prove degradation via staining of polypropylene meshes based solely on microscopic techniques. There is no chemical evidence of any degradation and the stain methodologies utilized are not based on sound, scientific principles and experimentation. Polypropylene does not accept stain.

Review of Dr. Scott Guelcher’s Oxidation Study

I have reviewed FTIR, SEM, and XPS data collected by Dr. Scott Guelcher, *et al*. in which he attempts to oxidize a polypropylene standard and TVT mesh, a product composed of Prolene just like the product at issue here, with a mixture of cobalt chloride ($CoCl_2$) and hydrogen peroxide (H_2O_2). Even though this method is reported to be an aggressive oxidation environment[294] NO OXIDATION of any Prolene mesh products could be determined by FTIR and XPS. These data support my contention that Prolene is a highly stable polypropylene based polymer and does not undergo scientifically significant oxidation or degradation *in vivo*. For instance, limited oxidation is shown in only two polypropylene control samples which do not contain antioxidants, unlike Ethicon’s Prolene, which is properly formulated with two, highly effective antioxidants.

The FTIR spectra of Figure 21 are taken from Dr. Guelcher’s data collected during his cobalt chloride ($CoCl_2$) and hydrogen peroxide (H_2O_2) oxidation experiment, and supports my opinion that Prolene is resistant to oxidation. For instance, no carbonyl groups were formed during the oxidation experiment, and thereby confirms the exceptional stability of Prolene to this aggressive oxidation environment. The spectra below in Figure 21 shows the 4 week polypropylene control sample (blue spectra) overlaid with the 4 week TVT sample (red spectra). Dr. Guelcher reports oxidation of the un-stabilized PP sample evidenced by the peak at 1736

cm^{-1}. However, no such peak is present in the TVT sample subjected to the same oxidation medium. Furthermore, the noise associated with the spectra casts all his data in doubt. As one will note, the baseline spectra are not properly adjusted as noted by the presence of carbon dioxide (CO_2) absorption, an atmospheric contaminant.

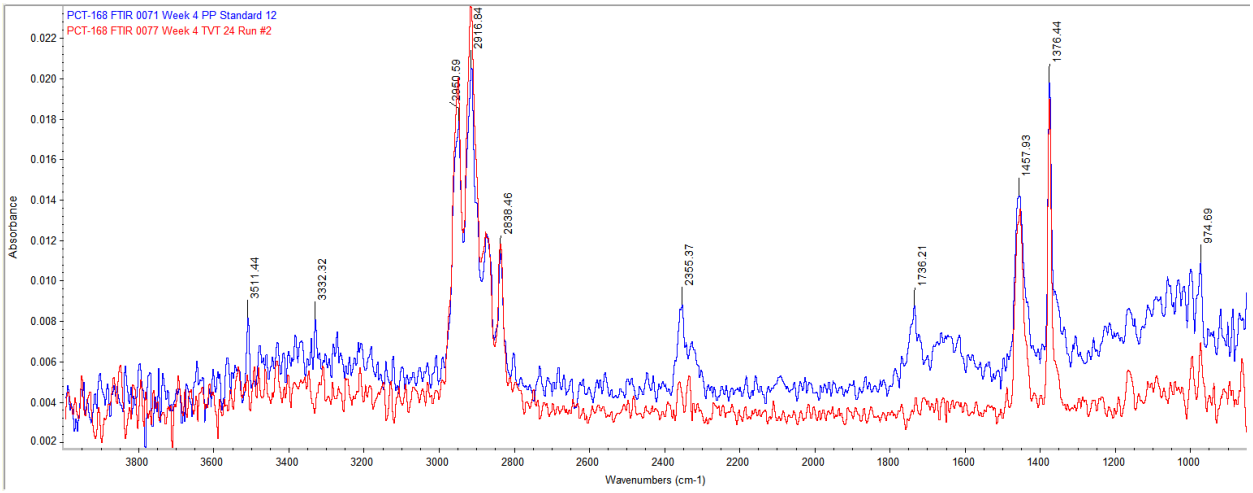


Figure 21. FTIR overlay of PP standard and TVT sample after 4 weeks in $CoCl_2/H_2O_2$.

Dr. Guelcher further opines, in the article entitled Oxidative Degradation of Polypropylene Pelvic Mesh In Vitro,[295] that oxidation is present based on an FTIR spectrum of TVT at 5 weeks, however no 5 week control spectrum is provided. His experimental data is not provided in sufficient detail to prove these claims. Therefore, his claim for Prolene oxidation should be dismissed as speculation, with no scientifically acquired supporting facts.

My inspection of his SEM photomicrographs suggests that the fibers were surrounded by deposited chemicals as their appearance is far different from the work of Dr. MacLean of Exponent.[296] Moreover, Guelcher's manuscript was void of any experimental efforts to remove the oxidation medium from the fiber surfaces. Simply rinsing in DI water is not sufficient. Dr. Guelcher's SEM analyses are likewise inconclusive, as they show nothing indicative of TVT mesh oxidation. While there is some contrast variation of the individual fibers surfaces, these are likely the results of $CoCl_2/H_2O$ deposited residues on the fiber surface during the drying step, in preparation for SEM analysis. These deposits could have been easily characterized by energy dispersive X-ray (EDS) analysis which would have shown the presence of cobalt, if it was present, while being imaged in the SEM. No such data was provided. In addition, the data set continues through a six week period for TVT samples, while the polypropylene control experimentation, and thus data collection, is provided for only four weeks. This represents a flawed, inconsistent, and inadequate scientific approach when experimental controls are not subjected to the same time period and treatment regime; and the results of testing data are not supplied. In any event, Prolene was not oxidized by the $CoCl_2/H_2O$ blend.

Dr. Guelcher's 'Methods' section regarding sample handling states that 'every week, 6 samples were removed, washed in DI water, and dried for analysis.'[297] Dr. Guelcher further notes that the samples were analyzed by XPS and FTIR in order to determine the presence of hydroxyl groups (-OH) and terminal C=O end groups.

Further analyses by X-ray photoelectron spectroscopy (XPS) analyses were performed in an effort to show Prolene oxidation. However, the experimental data does not support oxidation. The experimental data was collected by Dr. Bridget Rogers via XPS.[298] A review of Roger's Table 1 XPS data (Figure 22) for TVT is clearly flawed and in error. For instance, all samples of TVT should exhibit carbonyl configurations (C=O) as Prolene possesses DLTDP and Ca-Stearate, both of which are carbonyl (C=O) containing chemicals. However, Dr. Rogers found only 4 of 17 samples showed C=O configurations. These data clearly confirms the methodology used is flawed and in error, given all 17 samples of TVT possess carbonyl containing chemicals, and consequently the XPS data should confirm the presence of C=O for all samples, but does not. That Guelcher used this analytical technique to confirm C=O presence is proof positive he does not understand Prolene's chemical composition, yet he is opining on its potential degradation tendencies.

Table 1. Fraction of carbon atoms bonded in the R-C-OOH and C=O configurations on TVT samples

	TVT					
Week	First Sample		Second Sample		Third Sample	
	R-C-OOH	C=O	R-C-OOH	C=O	R-C-OOH	C=O
0	0	0				
1	0	0	0	0.0135	0	0
2	0	0	0	0	0	0
3	0	0	0.0088	0	0	0.00180
4	0.0106	0	0	0	0	0
5	0.4874	0	0.5054	0.0062	0	0.0084
6	0.0051	0				

Figure 22. Bridget Rogers XPS Data for TVT[299]

Even the polypropylene control pellets subjected to this oxidation do not show a consistent trend in C=O detected via XPS (see Table 2, week 1 Polypropylene Standard data) as noted in Figure 23.

Table2. Fraction of carbon atoms bonded in the R-C-OOH and C=O configurations on polypropylene bead standards

	Polypropylene Standard	
Week	First Sample	
	R-C-OOH	C=O
0	0	0.0108
1	0	0
2	0	0.0209
3	0.0110	0.0169
4	0.0176	0.0396

Figure 23. Bridget Rogers XPS Data for PP Standards[300]

Response to the Talley, Rogers, Iakovlev, Dunn, and Guelcher Publication

Plaintiffs' experts Scott Guelcher, Russell Dunn, and Vladimir Iakovlev along with co-authors Anne Talley and Bridget Rogers authored the following manuscript: "Oxidation and Degradation of Polypropylene Transvaginal Mesh" published in the *Journal of Biomaterial Science, Polymer Edition* 2017.[301] The five co-authors publishing the manuscript concluded they proved *in vivo* oxidation of mesh materials. I have reviewed the article and find numerous gross errors in data collection, data identification, and conclusions arrived at through misinformation. To the extent Dr. Guelcher relies on this paper in his expert report, these are my criticisms and will therefore include my analysis of this manuscript, and the numerous errors therein. The data collected by these 5 co-authors does not prove, by scientifically derived data, that Prolene is oxidized or degrades *in vivo*.

The publication did not include use of, or examination of, an explanted Prolene device. Experiments were performed on only one explant manufactured by American Medical Systems. The remainder of the specimens were pristine devices, and only one was an Ethicon (TVT) product.

The three pristine devices used were treated with 0.1 Molar solution of $CoCl_2$ in 20 weight % H_2O_2 *in vitro* as an oxidizing medium, purported by the authors, to simulate an appropriate concentration of *in vivo* reactive oxygen species (ROS). However, the authors have not provided sound, scientific, data to prove this assertion. Simply stated, they have not proved the concentration of *in vivo* ROS their experiment generates is equal to the concentration of ROS generated *in vitro by* Cobalt and hydrogen peroxide. Neither have they proved the concentration of ROS necessary to oxidize Prolene, *in vivo* or *in vitro*.

Given this significant scientific information void, the manuscript lacks factual data necessary to answer the question of *in vivo* ROS presence, concentration, and its potential degradation effects, if any, of *in vivo* mesh implants.

The authors failed to provide data necessary to answer the question of "what is the concentration, and what is the energy required for the ROS to oxidize any implanted polypropylene derived device;" let alone, antioxidant protected polypropylene such as Ethicon's Prolene derived products. However, Mittal and Babior[302,303] have reported an *in vivo* rate/concentration of ROS in response to the introduction of foreign bodies. The ROS generated by the Guelcher, *et al.* oxidizing medium of $CoCl_2$ in 20 weight % H_2O_2 derived radical would be a molar equivalent far exceeding that reported by Mittal and Babior. It is scientifically unrealistic therefore, to "assume", as did Guelcher, *et al.*, such a chemical concentration difference of an oxidizing medium is an acceptable scientific protocol; it is not. However, even the unrealistic concentration of Guelcher, *et al*. oxidizing medium fell short of oxidizing polypropylene or Prolene *in vitro*.[304] Additionally, it is reported that inflammatory response to foreign body phagocytic cells results in foreign body giant cells that coat the surface of the "material" and attempt to destroy the "material" with ROS, enzymes and reduced pH.[305] It is also reported that adherent macrophages cannot maintain an oxidative burst to continuously attack foreign body materials indefinitely. Therefore, the adherent macrophage exhausts its ability to continually attack the foreign body material.[306,307] Furthermore, it is reported this process is material specific regarding the length of time before macrophage cell apoptosis and exhausted respiratory attack of the foreign body.[308] Contrary to the authors' assertions, the *in vitro* assay used by the authors does not represent *in vivo* conditions with respect to a foreign body (i.e., an implant).

In summary, Guelcher, *et al.* have not considered the following critical elements of the supposed oxidation of a foreign body:

- ROS concentration *in vitro* greatly exceeded literature reported ROS production over the same time period,
- Factors unknown within the "privileged microenvironment":
    1. Concentration of ROS available in the microenvironment,
    2. Concentration of ROS required to oxidize a foreign body
    3. Concentration of proteins in the microenvironment,
    4. Volume of the microenvironment,
    5. Life span of the macrophage adhered to the Prolene fiber,
    6. Disposition of exhausted macrophage adhered to polymer fiber,
    7. Relative pH of the microenvironment,
    8. Oxidative burst respiration duration,
- Polypropylene's *in vitro* exposure morphology does not match *in vivo* explant morphology,
- The concentration of ROS necessary to chemically simulate *in vivo* conditions is unknown.

The **"In vitro oxidation assessed by FTIR spectroscopy"** portion of the Guelcher, *et al.* manuscript has serious scientific challenges, not the least of which is the improper labelling of "hydroperoxide" and "carbonyl" regions of FTIR spectra. For instance, the hydroperoxide region (black) and carbonyl regions (gray) as per the "*In vitro* oxidation assessed by FTIR spectroscopy" are mislabeled according to the manuscript text and are thus mis-assigned in Figure 2 of the manuscript and as noted in Figure 25 below. This article was accepted as peer reviewed, and therefore must have been approved for publication by Talley, Guelcher, Rogers, Iakovlev, and Dunn.

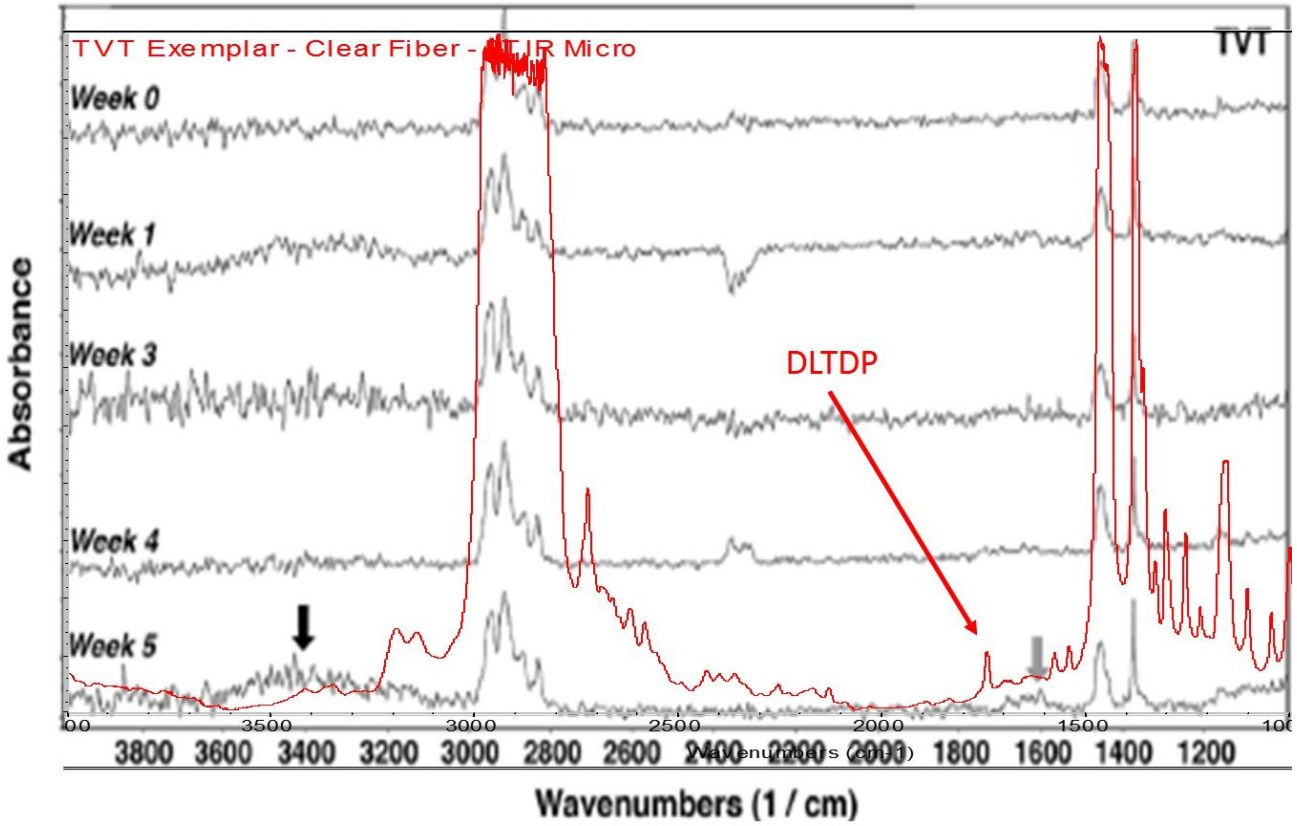


Figure 25. Excerpt of Figure 2 from the Talley, Rogers, Iakovlev, Dunn, and Guelcher Paper[309] overlaid with a TVT Exemplar Spectrum of Thames collected with 64 scans at 2 cm^{-1} resolution.

- Moreover, the quality of Guelcher, *et al.* FTIR spectral data are not scientifically sufficient lack sufficient to support their conclusions, and the poor spectral resolution and instrument baseline "noise" make spectral interpretation unreliable and prone to errant conclusions.
- The carbon dioxide absorbance at 2350 cm^{-1} is spectral interference of an impure atmosphere. The 2350 cm^{-1} peak assignments of CO_2 is a prominent, interfering absorption peak that should not be present. Its presence confirms a proper baseline configuration was not achieved. Proper baseline subtraction would remove the artifact peak, and enable more accurate interpretation of the spectra.

- The FTIR spectrometer method, resolution, and number of scans were not reported. Based on the baseline noise, very few scans were collected and based on generally accepted principles of FTIR spectroscopy, a greater number of scans would have greatly improved the spectral quality thereby making spectral assignments easier and more reliable.
- The poor quality of the spectral data is further diminished by the noisy background interfering with the peak absorptions of interest and proper assignment of peaks.
- The reported "oxidized" polypropylene peaks shift from week to week and between samples and is inconsistent with reliable scientific data.
- It is well known, and shown in my spectra, that Prolene contains DLTDP, a carbonyl functional group, which appears in my control FTIR data at 1740cm^{-1}. However, this same spectral absorption does not, but should, appear in the Guelcher, *et al.* Figure 2A TVT zero-week experiment, at the very least (see Figure 25).

Consequently, the Guelcher *et al.* FTIR data is misleading, inferior, and wrong; therefore, Guelcher, *et al.* spectral data should not be considered as significant nor valid.

- The absence of the DLTDP peak assignment from the zero-week TVT sample proves the inferiority of Guelcher, *et al.* spectral data and their interpretation thereof.
- The broad integration region of 3000 – 3600 cm^{-1} includes functional groups of formulated Prolene. It is well known that Prolene products, like TVT, are formulated with carbonyl containing antioxidants. However, the peaks associated with the TVT week zero control would also absorb in the region identified by Guelcher. However, Guelcher *et al.* have over-reached and identified all absorptions in the C=O regions as proving "oxidation." They are wrong.
- For instance, if an FTIR spectrum of an explant shows C=O spectral absorptions the explant is deemed to be oxidized *in vivo* by Guelcher*, et al.*, yet Prolene's chemical composition includes C=O components. Putting it another way, regions of the FTIR spectral data identified by Guelcher as showing oxidation (i.e. C=O) are also spectrally active regions for <u>pristine formulated Prolene</u>. Their presence therefore in an FTIR spectrum, cannot be used to confirm *in vivo* Prolene oxidation.
- Guelcher, *et al.* are either unaware of Prolene's chemical makeup or chose to ignore it. It is well known, to those familiar with mesh litigation, that Prolene is formulated with several ingredients including antioxidants, flow agents, and pigments. Therefore, there is no scientific proof to support Guelcher's, *et al.* claim of *in vivo* oxidation of polypropylene or Prolene. An explanation for the FTIR absorption peaks observed at week five and at no other time point is simply that the samples were not dry. Yet Guelcher, *et al.* utilize these week 5 data in an attempt to bolster their tenet of ROS oxidation of polypropylene and/or Prolene. Consider Figure 26 of the FTIR spectrum of water. [306]

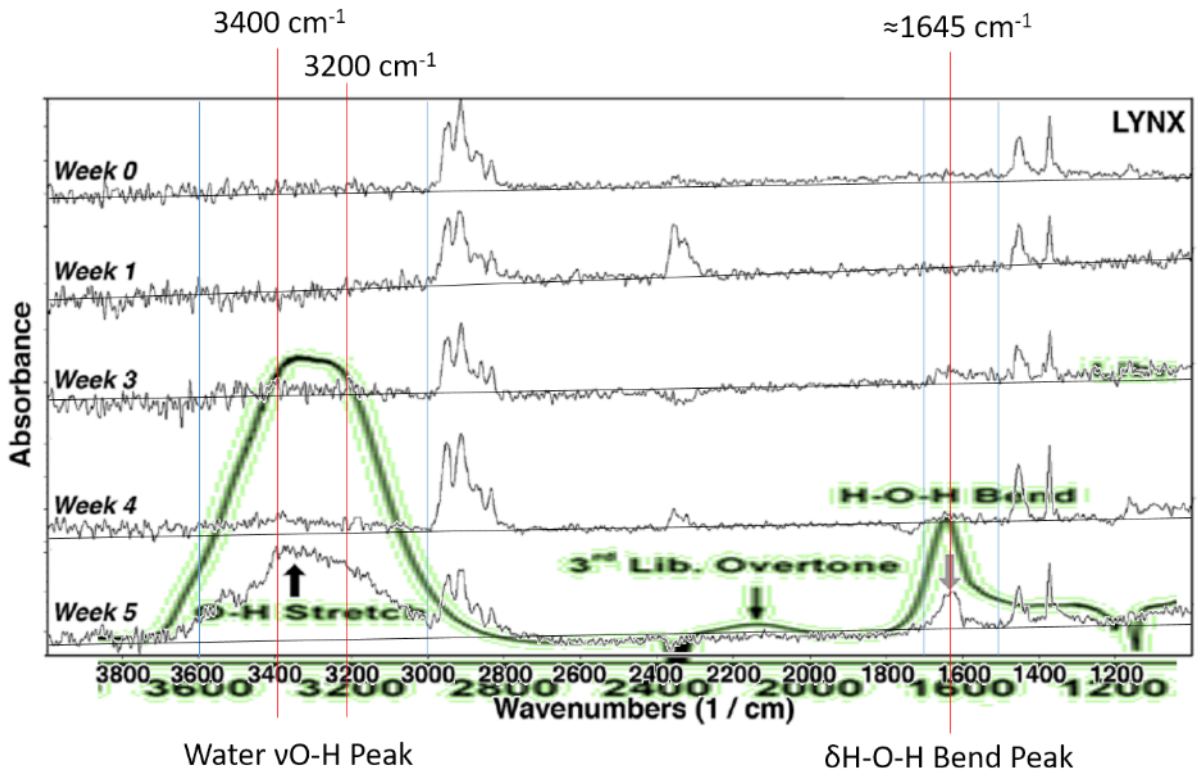


Figure 26: Compare the known FTIR spectrum of water to that of Guelcher, et al. The red vertical lines mark the expected and characteristic peaks from water sorption including the hydroxyl stretching peak between 3000 and 3600 cm^{-1} and the bending moment of water at 1645 cm^{-1}.[310] The blue vertical lines are the integration range Guelcher *et al*. chose for their data collection of Hydroxyl and Carbonyl functional groups. It is clear therefore that Guelcher, *et al.* have mis-assigned the water peaks in support of their proposition for Prolene oxidation.

- Thus, sample preparation is suspect as the results identify perfectly with known water adsorption frequencies. The Guelcher, *et. al.* manuscript states, "by using an established *in vitro* assay", they are correctly simulating the *in vivo* conditions experienced by polymeric mesh implants. However, nothing could be farther from the truth. For instance, the privileged microenvironment concentrations of ROS has not been established, proven or known, nor is it known in what volume these conditions occur.
- It is thought that radical hydroxyls are the main species in contact with polymer fibers, and that the oxygen radical is formed by breakdown of hydrogen peroxide *in vivo*. The half-lives of hydroxyl radicals are extremely short at 10^{-9} sec,[311,312,313] and therefore, the effective *in vivo* oxidative potential of the hydroxyl radical is unknown, when attempting to react with *in vitro* Prolene mesh implants.
- Literature cited by Guelcher *et al*. used a methodology that relies on post-exposure observations to correlate degradation in a different, unrelated polymer system to justify their concentration of ROS *in vitro*. The cited literature did not use the actual concentration of ROS in the microenvironment (because it is not known), but guessed

the *in vitro* concentration based on the result of chemical attack on the (non-Prolene) polymer mesh they used.

- If the authors believe the "established *in vitro* assay" was indeed a true simulation for the privileged microenvironment, then they should have followed the literature described methodology. However, Guelcher *et al.* doubled the concentration for ROS generation from recommended literature values.[314]
- Furthermore, the authors "refreshed" the solution of ROS every 3-4 days to increase the lifetime of the reactive oxidative species in their *in vitro* experiment. Throughout the Guelcher *et al.* experiment the reactant medium was refreshed approximately a dozen times, effectively increasing the total *in vitro* generated ROS, in contrast to the "established *in vitro* assay."
- Clearly there is no consensus regarding the true simulated microenvironment an implanted biomaterial experiences. However, Guelcher, et al. repeatedly state or imply the *in vitro* assay used to supposedly "oxidize" polymer samples supports the hypothesis that *in vivo* oxidation of polypropylene occurs. Guelcher, et al. have not proved polypropylene or Prolene oxidizes *in vivo*. In summary, consider the following:
- The morphology of the polymer post exposure does not match *in vivo* explant visual observations,
- No XPS or EDS data was provided to exclude Co fiber contamination,
- No established in vivo ROS concentration is known,
- No *in vivo* volume for ROS is known,
- No *in vitro* assay volume was provided by Guelcher, *et al.,*
- Authors incorrectly assume correlation is causation regarding visual observations,
- Authors use large excess of *in vitro* ROS to hopefully affect an *in vivo* conclusion.
- There is concern with respect to the validity of results reported, regarding the proposed rate of oxidation. Chemical reactions progress in a defined state based on the reactivity or speed of conversion,[315] and yet Guelcher, *et al.* are suggesting there is no chemical reaction of any of the polymer samples until week 5, and no explanation is provided.
- They are essentially saying that the radical reaction, with a half-life of 10^{-9} seconds[316,317] remains dormant for five weeks. Theirs is not sound logic. Nor is it consistent with cobalt chloride-hydrogen peroxide oxidation of polypropylene or Prolene.
- Their chemical rates do not follow any known reaction mechanism of which I am aware. Guelcher and colleagues are clearly confused with respect to the assignment and collection of their FTIR data. For instance, on two separate occasions the authors identify the hydroxyl peak as the carbonyl peak and the carbonyl peak as the hydroxyl peak. It should be noted that the stated integration of the peak areas were consistent with the correct expected absorptions (Guelcher *et al.* Fig. 2 legend p. 11); however, the reported data for the area integration are not consistent with the correct peaks (again, they have it backwards). It is inconsistent with scientific rigor to incorrectly identify a major component central to the argument of the thesis.
- Their argument attempting to correlate *in vitro* experiments to the argument made for *in vivo* "oxidation" of polypropylene or Prolene fails, when the reader realizes the authors have misidentified FTIR absorption frequencies on two occasions. One, at first, might think it a typographical error. However, the integration of the peak areas was also transposed. Given the poor data quality, and gross data misinterpretation, the integrity of this work is suspect, lacks scientific rigor, even though it was peer reviewed. Surely any

serious peer review process would recognize such gross errors as misidentification of major spectral regions, such as the difference in the hydroxyl and carbonyl regions.

- Peak identification for FTIR results *in vitro* were incorrect on two occasions
- Integration was reported for the wrong peaks, again incorrect,
- Gross data misinterpretation beyond acceptable scientific rigor,
- Poor data quality with respect to spectral noise interfering with integration,
- Peer review process failed to identify these gross errors in the manuscript,
- All five authors failed to correctly identify the peaks associated with the specified functional groups. Guelcher *et al.* show several SEM micrographs to support the postulation that polypropylene degrades *in vivo* after exposure to a radical oxidation medium *in vitro*. It should be noted that the SEM micrographs bear no resemblance to the many previously reported images of explanted polymer mesh samples. This fact was acknowledged by Guelcher *et al.* in the discussion saying "[we] did not reproduce the transverse cracking observed for explanted PP sutures and mesh *in vivo,*" which is the most obvious reported features typically reported for unclean explanted mesh samples fixed in formalin solution.
- Guelcher, *et al.* did not report how depth measurements were calculated in the SEM micrographs. The pit sizes reported were not consistent between samples. No explanation or acknowledgement to this inconsistency was provided. We have analyzed more than 90 explants and have never seen pitting or flaking of Prolene explants.
- SEM micrographs do not represent previously observed explant images,
- Authors failed to provide pitting measurement techniques,
- Authors failed to discuss the lack of similarities with Dr. Thames' cleaned fibers and the mechanical extrusion markings typically observed on new polymer fibers,
- Authors incorrectly correlate SEM visual results as causation of *in vivo* explant observations.

Guelcher *et al.* mechanical manipulation to avoid cleaning

The authors utilized XPS, which has been shown in past work to be a flawed method in the hands of Guelcher, Dunn and Rogers.[318]

- The authors referenced valid carbon 1s bond energies yet made no comments regarding deconvolution. The following describes polypropylene as a deconvolution of two separate carbon bond energies i.e. $-CH_2$ and -CH. The bond energy ratio is 67% to 33% (Figures 27 and 28).

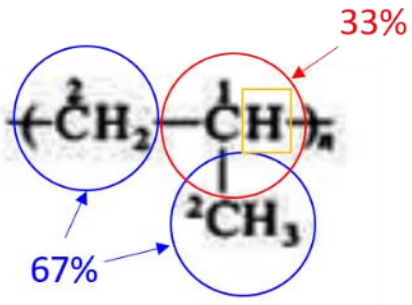


Figure 27: Structure of Polypropylene unit with carbon bond types indicated. Blue circle indicates –CH_2 carbon 1s bond energy type and the red circle indicated the –CH carbon 1s bond energy type. The yellow square indicates the carbon-hydrogen with the lowest bond energy.[319]

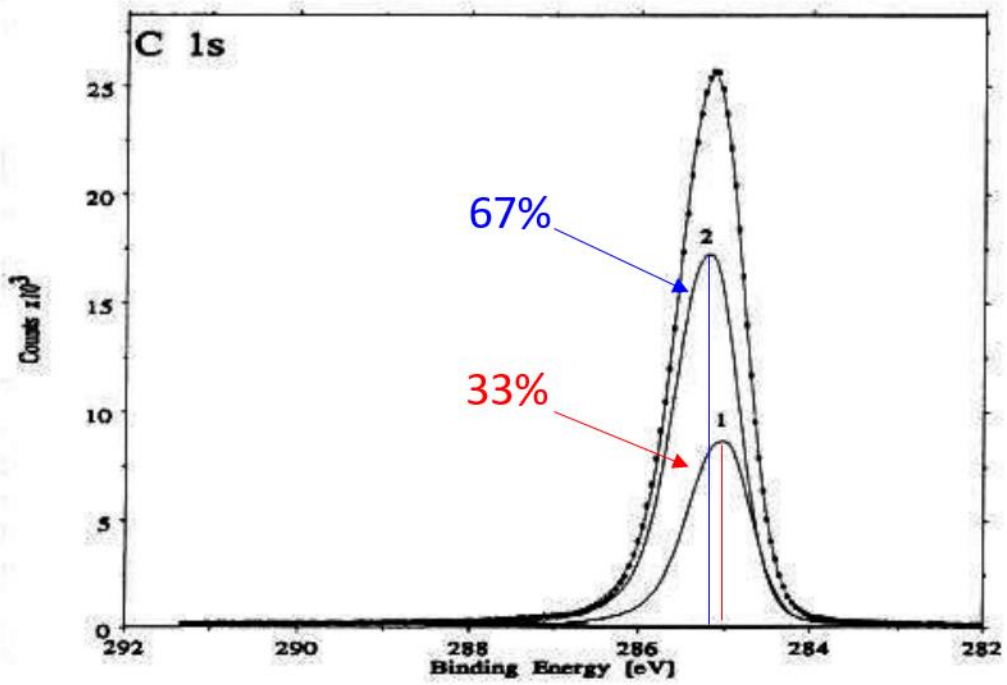


Figure 28: Deconvolution for polypropylene carbon 1s bond energy for pristine polymer material containing no additives. The blue line indicates the slightly higher bond energy of the carbon 1s –CH_2 chemical bond. The red line indices the slightly lower bond energy of the carbon 1s –CH chemical bond. The deconvolution ratio for polypropylene as a material characteristic is always 67% to 33% carbon 1s bonds.[320]

Without establishing these ratios of carbon bond energies using a control, it is not possible to claim the data collected is relevant to the polypropylene polymer fiber. Because only one sample (sample #17) indicated a peak specific ratio for carbon bonds (albeit incorrect – a 67:33 ratio was not shown), it is easy to conclude that the XPS data was collected on the total material present and not just the polymer fiber. Their collection of XPS on a fiber surface for analysis, and neglecting adhered flesh, erroneously included other-than-polymer carbon bond energies. Therefore, data gathered in this way clearly does not and cannot support the claim of *in vivo* polymer oxidation. Furthermore, Guelcher *et al.* flawed methodology did not use a polymer fiber to calibrate, verify, validate, or function as a control for the XPS's data.

Cutting or mechanically challenging a polymeric material results in chain scission as chain scission occurs when polymer bonds are broken by mechanical methods without regards to their position in the polymer chain. It is not possible to cut polymer material without disrupting or breaking chemical bonds. Mechanically cutting a polymeric material results in lower molecular weight polymers that may have radical terminated un-paired electrons, i.e. radical electron that will react in its local environment to abstract a nearby proton, react with oxygen, and/or

water.[321] Regardless of the reaction pathway, the radical electron's final product will be a carbonyl-containing or hydroxyl functional group.[322] Therefore, the proposed "core oxidation" observed could just as well have been a result of cutting the polymer fiber.

- No control polymer fiber was analyzed to exclude the possibility of radical formation by mechanical chain scission.[323] Without a control, one ignores the possibility of degradation by mechanical assault and thus the Guelcher, *et al.* data, does not meet the basic scientific rigors to be considered valid.
- Cutting a polymer with a knife can form radicals that result in carbonyl or hydroxyl functional groups,
- No control fiber was analyzed to account for the possibility of radical formation,
- No control series was performed to define the instrument precision or sensitivity.

Guelcher *et al.* have criticized my cleaning protocol and introduced a "new" cleaning method using a formalin-free explant sample. Most specimens prepared for pathological analysis are fixed in formalin. Without the protein-formalin polymer adhering to the fiber surface, a required cleaning procedure would be much less rigorous than those reported in literature. Anything less than a complete removal of tissue components from the surface will result in erroneous analysis of the specimen. Furthermore, Guelcher, *et al.* contend that sonication cannot distinguish between adhered proteins and "oxidized" polypropylene surfaces, while at the same time they argue that manual scraping with a scalpel can distinguish between these two materials and physically separate them. Indeed, it is illogical to assume or accept that a scalpel with a width similar to the width of a polymer fiber can successfully distinguish, and reproducibly separate adhered protein from the polymer surface by the human hand and a dissecting microscope. Consider, for example, Figure S1 of the Guelcher *et al.* supplemental data where five scraped samples show no similarities. It should be further noted that the surface morphology of the scalpel is straight while that of PP mesh is round. With the scrape interface mismatch (round vs straight), it is no surprise the authors advocate for additional testing of their unproven, radical methodology. A round fiber and a straight blade do not make for a clean scrape of the fiber surface in an effort to selectively remove adhered flesh from the polymer-tissue interface.

- Method proposed is not reproducible, and therefore, not open for challenge by the scientific community as a disprovable hypothesis,
- Cleaning method by sonication was not disproven,
- Criticism of sonication is not valid as the authors have not proven that *in vivo* oxidation of Prolene occurs; therefore, no oxidized Prolene is lost in cleaning.
- Authors repeatedly argue that oxidation has occurred on the polymer fiber, but have not shown a single explant fiber that is tissue-free and contains carbonyl (C=O) oxidation species.

More alarming is the egregious mislabeling and mis-assignment of data and apparent lack of data integrity. Regardless of the previous shortcomings of scientific rigor in this paper, there seems also to be an incident of data fabrication. For instance, in Table S6, Fiber # 5 and 8 report R-C*COOH values NOT present in the XPS spectrographs, Figure S2. The reported values of 2.5 and 2.3 for Fibers # 5 and 8, respectively, are not represented as a bond energy

in the deconvoluted peaks for those samples. The remaining peak percent values in table S6 are correct and in the correct column, so this is not a typographical error in the data. It appears these values or numbers were "placed" in the table to validate the author's claims of polypropylene oxidation *in vivo*. Moreover, these data are used specifically to generate Figure 4E, which is the single major datum used to support the author's claim that the polymer fibers undergo degradation *in vivo*. The author's twice talk about these specific data points in Table S6 and opine about their significance to the degradation of polypropylene. Interestingly, if those seemingly fictitious data points are removed and the values recalculated (using their methods), then the resulting value would have an error greater than the mean at 0.8 ±1.2 peak percent. Therefore, the resulting data would have the probability of being less than zero, and would be considered insignificant noise. Causation for the seemingly inserted, falsified data in the column labeled R-C*COOH was obligatory to support the proposed polypropylene degradation model. Without bonds present in the "stable intermediate" of the hydroperoxide, the mechanism is not valid because the hydroperoxide bond must occur before the carbonyl bond. Inserting data in Table S6 was required to validate the model proposed. Additionally, the result total for the $–CH_2$ peak area was transposed with –CH peak area percent as stated above. It should be of note that adding the additional false data into the column for Fibers #5 and 8 would require balancing the total peak area to 100%. Balancing the areas require changing the numerical summation for each column to account for the added values in the R-C*COOH column. In haste or otherwise, the values for $–CH_2$ and –CH were not correctly balanced and seems to have been transposed without double checking the result beyond adding to 100%.

Response to Dr. Jimmy W. Mays Reports

I have reviewed Plaintiff's expert report and have the following comments.

Plaintiff's expert data is referenced herein as the Imel, Malmgren, Dadmun, Gido and Mays 2015 Biomaterials manuscript which has been cited several times.[324] In drawing conclusions Plaintiffs expert cites the works of Liebert, Mary, Clave, Costello, Ostergard, Bracco, and Iakovlev. With the exception of Bracco, I have responded to the writings of the remaining authors, in this and other reports, but will add, for some, additional comments herein.

I have also reviewed and commented on the Rule 26 Expert Report of Jimmy W. Mays, dated May 22, 2017 Relating to Wave 5.

Plaintiffs expert refers frequently to polyurethanes in an attempt to relate polyurethane (PU) chemistry to polypropylene (PP) chemistry, although they are <u>completely different</u> polymer types. PP is composed exclusively of carbon and hydrogen while polyurethanes include carbon, hydrogen, oxygen, nitrogen and a myriad of other elemental species. Therefore, the chemical reactions of PP and urethanes are quite different and should not be used on a comparison basis, although the writings of Mays and Guelcher continue this erroneous practice. For instance, PP is a hydrocarbon, is totally non-ionic in character while polyurethanes are polar and ionic, as they possess elements and functional moieties of very differing electronegativity and composition.

I will frequently comment to Dr. Mays' statements, by providing a statement/response such as:

Statement: Mays statements begins and continues throughout speaking of polypropylene, while giving little consideration or factual information about Prolene, the formulated polymer and subject of this litigation. Consider for instance, his first summary of opinions statement, "It has been well understood for many years that polypropylene is susceptible to oxidation and it degrades by an oxidative mechanism in the body, resulting in chain scission and diminished mechanical properties (reduced compliance and brittleness). These facts are clearly documented in the peer reviewed scientific literature. Ethicon did not take into account polypropylene's propensity for oxidation during design of its various Prolene based mesh products."

RESPONSE: These statements are constructed to confuse the reader. Consider the following, well established data. Ethicon's Prolene, the subject of this litigation, is a formulated product consisting of six ingredients, (1) polypropylene (PP), (2) Santonox R, (3) Dilauryldithiodipropionate (DLTDP), (4) Calcium Stearate, (5) Procol LA, and (6) blue pigment. Each ingredient was chosen to provide a certain property, and in the case of the antioxidants, Santonox R and DLTDP, they were chosen as an effective duo of antioxidants to work in synergy to protect PP from degradation during the manufacturing process and during the product's lifecycle. Certainly the issue of oxidation was considered by Ethicon during the design and formulation of Prolene. Accordingly, Ethicon did, in fact, take into account PP propensity for oxidation during design and formulation of its various Prolene based mesh products with the incorporation of DLTDP and Santonox R. The facts prove it to be so.

Statement: The mesh is intended to last for the lifetime of the patient, but the addition of antioxidants to the Prolene polypropylene does not permanently prevent mesh degradation, and thus it is not possible to guarantee that the mesh will function properly after implantation.

RESPONSE: Ethicon formulated Prolene to last and it has done so in the almost 100 explants I have examined and tested. In none of these cases have I found oxidized Prolene using Light microscopy (LM), Scanning Electron Microscopy (SEM), or Fourier Transform Infrared Spectroscopy (FTIR). In particular, no oxidation derived carbonyl groups were found after flesh removal from the Prolene explants. The mechanism of oxidation in Dr. Mays' report specifies that carbonyl formation must occur if oxidation takes place. Therefore, the absence of carbonyl groups on the surface of Prolene explants confirms that oxidation of Prolene did not occur *in vivo*. Nor have I seen any other evidence that Prolene is subject to meaningful oxidation or degradation in the human body.

Statement: "Ethicon was aware of the oxidation of Prolene prior to the introduction of the transvaginal mesh devices sold by Ethicon to the marketplace,---"

RESPONSE: This statement by Dr. Mays has no substance, in that to date, I am unaware of any meaningful scientific data that confirms carbonyl group formation of Prolene. And, it has been established that carbonyl groups must be formed if degradation of Prolene has taken place. Dr. Mays is incorrect in this assessment and understanding of Ethicon's Prolene

supposed oxidation. How could Ethicon be aware of Prolene oxidation if oxidation has not been proven to occur. Dr. Mays is wrong.

Statement: “Foreign body reaction to the mesh *in vivo* leads to oxidation, chain scission, reduction in molecular weight, embrittlement, degradation, flaking, pitting, and cracking;”

RESPONSE: Once again, this statement has no factual basis. For instance, oxidation, chain scission, reduction in molecular weight, embrittlement, degradation, flaking, pitting, and cracking can and will only occur if oxidation produces carbonyl groups, and chain scission ensues. To date, there is no reliable data supporting carbonyl group formation of which I am aware, and I emphasize “no reliable and repeatable scientific data.”; I have examined and evaluated almost 100 explants and no carbonyl groups were found via FTIR spectroscopy.

Statement: PP mesh is not inert and its properties change after implantation, which can lead to adverse events in an implantee.

RESPONSE: While I am unaware of any completely inert material, as I have stated in all my general reports, I am unaware of any change in Prolene properties while *in vivo* that had or produced adverse effect(s) on Prolene. To the contrary, plasticization of Prolene during *in vivo* periods of up to 7 years did not adversely affect Prolene but did improve its toughness, as proved by Dan Burkley’s 7-year dog study of tensile strength and elongation data.[325] The Burkley data supports long term durability of Prolene in that physical properties improved, no meaningful molecular weight losses were documented, and no oxidation derived carbonyl groups were found. In summary, the Burkley data supported the thesis for long term viability of Prolene *in vivo.*

Statement: Thus, the Prolene mesh is unreasonably dangerous, defective and is not suitable to serve as the permanent implants that they have been represented by Ethicon to be.

RESPONSE: I do not believe Prolene mesh to be dangerous, defective for its intended use, or unsuitable as represented by Ethicon. I base this statement on my years of study of Prolene explants, my testing of almost 100 Prolene explants, and the data obtained from LM, SEM, and FTIR spectroscopy tests. In no instance have I collected data that would support Prolene oxidation *in vivo.*

Statement: Dr. Mays writes in his May 22, 2017 report that, “Strong evidence suggests that the process of enzymatic degradation of polypropylene involves a free radical oxidative mechanism, the same as or analogous to those shown above, with oxygen being incorporated into the polymer, first as hydroxyl groups and then as carbonyls.”

RESPONSE: Irrespective of supposed strong evidence suggesting free radical oxidative degradation of Prolene, there is no documented, scientific factual data collected, of which I am aware, that proves free radical or oxidative degradation of Prolene *in vivo.* Dr. Mays has not provided any such data, only suggestions without data, and my testing of Prolene explants are facts in evidence in support of my opinion.

Statement: Macrophages on the surface of the material fuse to form foreign body giant cells (FBGCs), resulting in secretion of high concentrations of highly reactive oxidizing species (peroxides, acids, enzymes) on the surface of the implant [13]. This foreign body reaction persists at the surface of the implant as long as the implant is in the body [13]. Thus polypropylene, which is known to be susceptible to oxidative degradation, is continually attacked by strong oxidizing agents inside the body.

RESPONSE: There are several available journal articles which contradict Mays statement. Mays identifies macrophages adhered to the polymer fiber explanted for analysis. What is not discussed is the respiratory response of the macrophage upon frustrated phagocytosis. Once the macrophage adheres to the polymer fiber, it undergoes a burst respiration releasing ROS, enzymes and reducing the pH of the intimate interface between the polymer and the cell.[326] Once the adhered cells are exhausted of their respiratory response, the macrophage is left almost or completely incapable of attacking the foreign material with ROS.[327] Furthermore, the cells adhering to hydrophobic foreign material (Prolene) undergo apoptosis in as little as seven days from the time of cell adhesion.[328] The material properties (i. e. differences between polymer types) of the foreign body affect the rate of cell adhesion and cell death in the local environment around the foreign body material.[329] Furthermore, cells that do not undergo apoptosis function at a reduce capacity for attacking the foreign material.[330] Mays once again, has not provided scientific evidence supporting his tenet that identified macrophages, proteins, or FBGSs are active and maintain the capability of continued respiratory attack of the foreign material at the levels he postulates can cause oxidative damage to Prolene. Indeed, the cells adhered to the polymer fiber, along with excreted proteins and other cellular components, are what I believe are cleaned from the explanted mesh materials. We know the bond between the fiber and phagocytic macrophage is tight and requires aggressive cleaning with or without formalin fixation. Indeed, it is this proteinaceous cellular material Mays describes as adherent macrophage that, when removed from the host and dried, is cracked and has been consistently, incorrectly described as degraded mesh;[331] It is not.

Statement: Oxidative degradation of polypropylene causes chain scission – it literally breaks the polypropylene molecules apart. This degradation causes a reduction in the mechanical properties (resistance to breaking under load or strength) of the polypropylene since mechanical properties decrease when molecular weight is reduced [7,15]. Furthermore, the degradation starts at the surface of the implant where it is in contact with its surroundings, and the disordered amorphous regions of the polypropylene are particularly susceptible.

RESPONSE: This is a very lucid statement by Dr. Mays teaching the jury what must happen if Prolene is oxidatively degraded *in vivo.* However, he fails to teach the jury that no evidence exists for reduced mechanical properties, or for chain scission. Thus, Dr. Mays continues to have no evidence or real data, only rhetoric, of Prolene undergoing oxidative degradation or reduction in mechanical properties.

Statement: It should also be noted that oxidation occurs at the surface of the material where it comes into contact with oxygen or oxygen containing substances.

RESPONSE: Surely if oxidation occurs at the surface of the material (in our case Prolene) where it comes in contact with oxygen or oxygen containing substances, it would be detected by FTIR spectroscopy or SEM, and perhaps LM. However, Dr. Mays has not provided any such data to support this statement, and thus his comments must be dismissed from a scientific perspective. I, on the other hand, have provided laboratory derived LM, SEM, and FTIR data of many explanted Ethicon products. These data do not support May's opinion for oxidative *in vivo* degradation of Prolene.

Statement: Very recently Imel *et al.* [25] reported a study of *in vivo* degradation of polypropylene pelvic mesh (Boston Scientific) using methods specifically chosen to test whether or not oxidative degradation is responsible for observed changes in the mesh upon implantation.

RESPONSE: Imel, Malmgren, Dadmun, Gido, and Jimmy Mays did not use Ethicon's Prolene in this study.

Statement: Furthermore, Wood *et al.* [40] recently studied explanted hernia meshes composed of polypropylene, poly(tetrafluoroethylene) (PTFE), and poly(ethylene terephthalate) (PET), taken from a single patient, in order to compare physicochemical changes in these different mesh materials in the same host. They found strong evidence of oxidation of polypropylene by FTIR, as well as crazing and cracking by SEM. In contrast, PTFE and PET showed only slight chemical changes.

RESPONSE: Wood did not use Ethicon Prolene and it is unclear whether the PP product he tested was formulated with antioxidants.

Statement: "Claiming that all the prior peer reviewed studies on explanted polypropylene biomaterials cited above had used inadequate cleaning procedures to remove fixated flesh from the implants, and that the SEM images published (and discussed above) showing surface cracking, pitting, and flaking could all be attributed to a formaldehyde crosslinked protein surface layer of fixated flesh, Thames *et al.* [41] published a 23-step cleaning procedure including heating the samples to 70-80 °C in water several times, exposure to bleach solutions several times, exposure to enzyme solutions, desiccation several times, and repeated extended ultrasonication. After treating explanted polypropylene mesh with this extreme cleaning procedure, a smooth non-oxidized surface was found [41]" and "The extreme procedure of Thames *et al.* [41] which involves several ultrasonication will remove the oxidized layer and any polypropylene crystals contained in the oxidized layer."

RESPONSE: Dr. Mays, again, has no scientific data to support his theories of the Thames cleaning procedure. There is no scientific evidence that the Thames cleaning process alters the explant in any way so as not to obtain an accurate assessment of the condition of explanted Prolene. The argument that ultrasonics is too aggressive and removes oxidized Prolene has no bearing in fact, again only rhetoric. For instance, there have been several cases where the cleaning process used has cleaned the mesh in the first cleaning step, and has not been subjected to ultrasonics. Moreover, these examples complete the cleaning process of five cleaning steps including the use of ultrasonics. In none of these examples are there evidence of

the oxidation of Prolene or the removal of carbonyl groups that “might” be on Prolene. I have included a laboratory derived spectrum of one of these cases as an exemplar describing the entire cleaning process and the results I have obtained. Please note that none of the cleaning steps, including ultrasonics, have materially changed the explant and adversely affected it surface or any part thereof. If any changes in the Prolene explant were made such as oxidation, FTIR analyses would document the changes. Examination of Figure 29 proves after the initial cleaning (“After Cleaning Cycle 1”) there are no documented changes in the FTIR spectra as the explant makes its way throughout the remaining 4 steps of the Thames cleaning process. Thus, the comments of Dr. Mays espousing Prolene oxidation and/or removal of oxidized Prolene by aggressive ultrasonics, are again without scientific evidence. As additional evidence supporting the efficacy of the Thames cleaning process are the SEM data of Figure 30 below. Additionally, the six SEM photomicrographs provide visual evidence (data) that Prolene’s journey through the Thames cleaning protocol does not damage, oxidize or otherwise adversely affect explanted Prolene in any way. Indeed, the extrusion lines from the manufacturing process are still visible on the surface of the Prolene fiber.

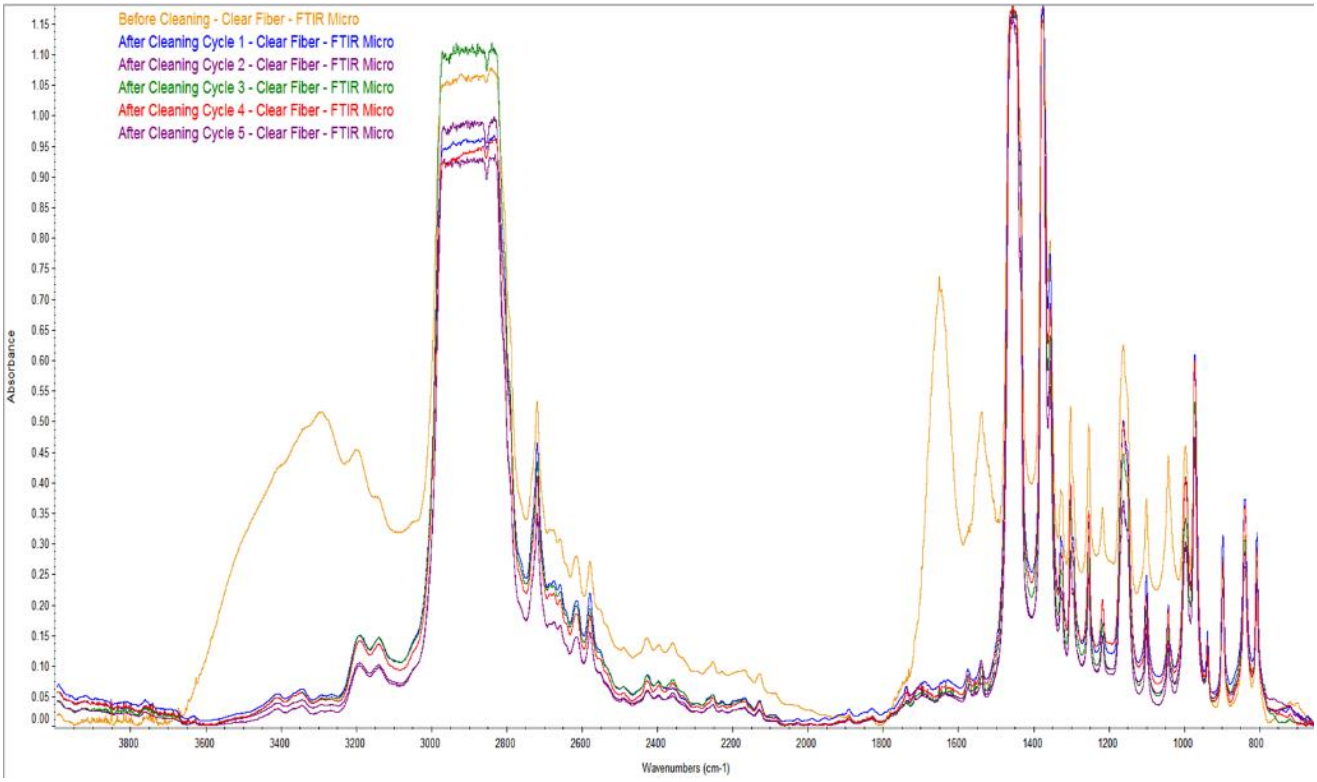


Figure 29. Patient Explant FTIR for Thames 5 cleaning cycles as compared to the “Before Cleaning” FTIR spectrum.

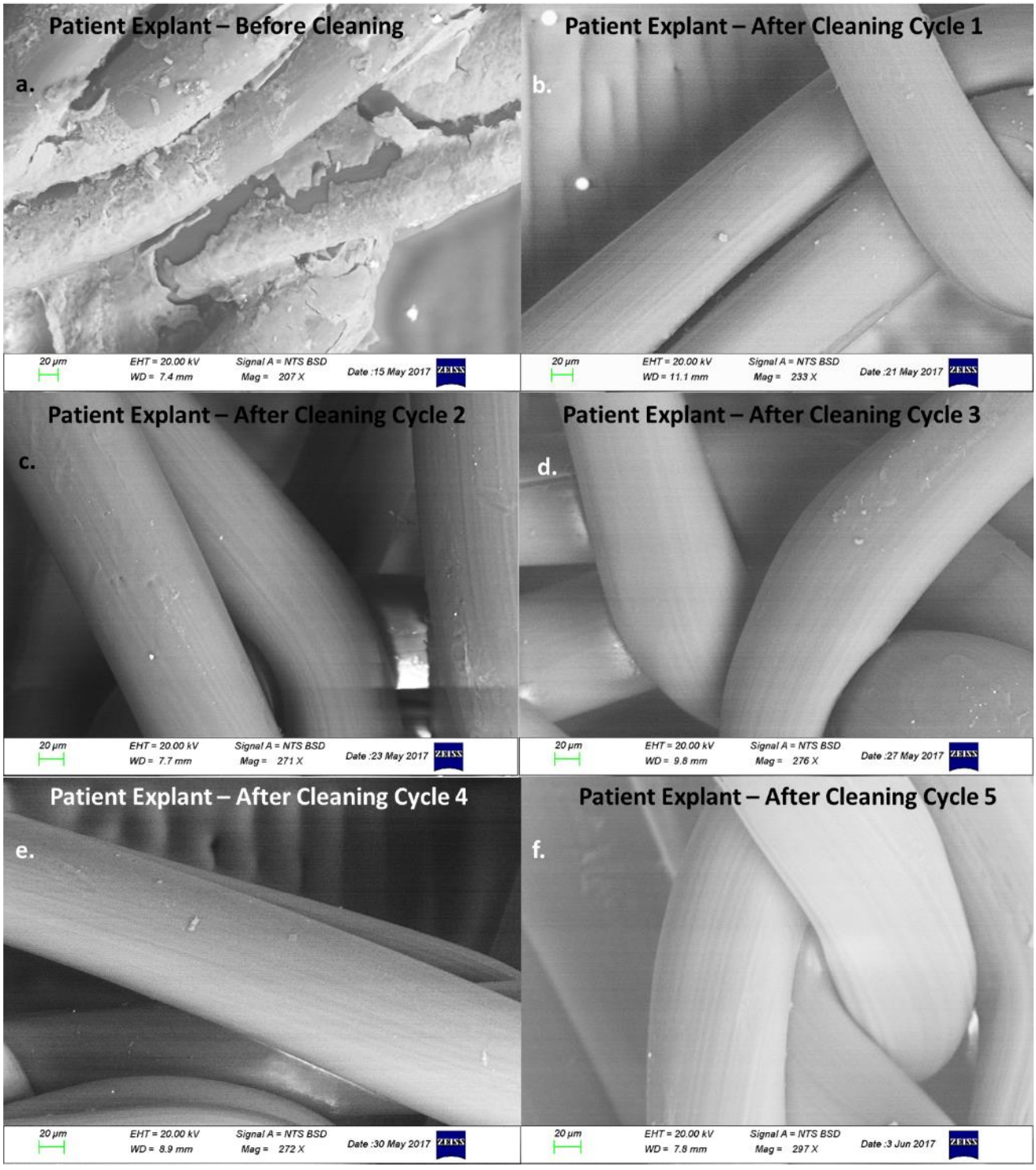


Figure 30. Patient Explant SEM for 5 cleaning cycles compared to the before cleaning explant

Statement: “Iakovlev and Guelcher [26] avoided use of a cleaning protocol entirely in their study by simply studying cross sections of explanted mesh without removing the tissue. This approach allowed them to avoid issues with tissue removal and revealed a non-degraded polypropylene core surrounded by an oxidized polypropylene “bark”.”[332]

RESPONSE: The decision not to clean explants at all simply means that non-cleaned explants will contain formalin-fixed tissue surrounding the explant, thereby assuring the presence of a porous, brittle and hard layer of fixed-proteins on Prolene’s surface, if immersed in formalin solution. If the explants are not “fixed” in formalin, flesh proteins will be firmly adhered to Prolene fiber and without removal will, upon drying, turn into dry and cracked protein laden surfaces adhered to Prolene. Any remaining “fixed” or “not fixed” proteins will remain on the Prolene appearing as adhered and likely dry flesh. This layer of fixed proteins adhered to the surface of Prolene will interfere with any subsequent effort to study the explanted mesh surface.

Statement: While there is no ASTM or ISO standard protocol for cleaning polypropylene implants, ISO 12891 recommends sodium hypochlorite (bleach solution) for cleaning the chemically closely related polymer ultra-high molecular weight polyethylene. Bleach cleaning was generally employed for removal of adhered tissue in prior work with polypropylene mesh implants [22-25,33], although Mary et al. [21] used an enzyme treatment, which like bleach solution, hydrolyzes peptide bonds breaking down the protein coating

RESPONSE: Dr. Mays references are supportive of the work of Mary, *et al.* while highly critical of the Thames cleaning protocol. However, it is ironic that the Thames cleaning process utilizes bleach as prescribed by ISO 12891 to clean hydrocarbon polymers and Mary uses an enzyme treatment as does the Thames cleaning process. Dr. Mays cannot have it both ways, but of course, he has no method of cleaning explants.

Statement: Very recently Iakovlev and Guelcher [43] published another study where in vitro treatment of polypropylene meshes (Ethicon and Boston Scientific) for 5 weeks resulted in the appearance of strong bands in FTIR associated with hydroxyl groups and carbonyl groups.

RESPONSE: This is the article of Talley, Rogers, Iakovlev, Dunn and Guelcher, “Oxidation and Degradation of Polypropylene Transvaginal Mesh,” in J. of Biomat. Sci. Polym. Edn., 28(5), 444-458 (2017). I have responded to this publication elsewhere in this report and will not repeat my work herein.

Statement: In response to criticism of his 23-step cleaning technique by plaintiffs’ experts, Dr. Thames carried out intentional UV oxidation of Prolene polypropylene mesh (Gynecare TVT device 810041B). In his report Dr. Thames shows an FTIR spectrum for the exemplar before Xenon exposure. A sharp peak at 1742 cm^{-1} is observed in the spectrum. This is in the region where carbonyl peaks, indicative of oxidation, occur. Thus it seems that this Prolene-based exemplar became oxidized on storage.

RESPONSE: I have responded to Dr. Mays assertion that during my response to plaintiffs’ criticism of my cleaning process, I reported the presence of a sharp peak at 1742 cm^{-1} in the spectrum. I have reported my reply to this illogical assertion elsewhere, but deem it appropriate

to once again respond. I am concerned that in Dr. Mays apparent need to find my work in error, he does not know, chooses to forget, or attempts to confuse the reader of this document. For instance, Dr. Mays has written that he knows DLTDP absorbs at 1742 cm^{-1} and that DLTDP is an ingredient of Prolene. Why then would he make the statement "Thus it seems that this Prolene-based exemplar became oxidized on storage." Surely he understands in this intentional oxidation of Prolene study the DLTDP antioxidant will diminish in concentration due to the strong UV irradiation over time. Finally, my report states, "The absorption frequency at 1742 cm^{-1}, indicative of Ethicon's DLTDP antioxidant, is also noted in my previous reports, which I rely upon, and is present in the spectrum.

Statement: Then the oxidized exemplar was cleaned, not by the 23-step protocol published by Thames et al. [41] but by immersing it in sodium hypochlorite solution (bleach) on a shaker for 30 min, removing it, and drying it. The FTIR spectrum was essentially identical to the FTIR of the oxidized specimen. Dr. Thames then claims "the cleaning protocol of Figure 1 did not remove oxidized carbonyl moieties from Prolene." However, Dr. Thames never applied the 23-step protocol of his Figure 1 [44]. He applied the same type of bleach treatment used by others in this field to clean polypropylene implants of tissue, while leaving oxidized polypropylene intact on the surface of the fibers

RESPONSE: Dr. Mays again, does not understand or intentionally attempts to confuse those who are involved in this litigation with respect to my intent and timing of the "Intentional Oxidation of Prolene Mesh, Supplemental Report of Dr. Shelby F. Thames, August 8, 2016". Given my efforts to be completely transparent with my supporting data, it was determined to intentionally oxidize Prolene and study the process and product produced with time. Plaintiffs' experts opined that the 23 step explant cleaning protocol I developed and used during the examination of samples in this litigation, had in some way destroyed oxidation carbonyls should they exist. The cleaning process began and continued through "After Cleaning 4" at which time this report was written. This fact was explicitly stated, "The oxidized Prolene exemplar is currently being processed through the cleaning steps of Figure 1 (my 23 step procedure), and that data will be reported when complete. At this writing we have completed steps 1 through 4 and these data are reported herein. Our experience to date has shown these first 4 steps to be those during which the majority of the proteins are removed, and if there is Prolene oxidation these are the steps where oxidation would most likely be observed." I then followed with a paragraph reserving my rights to supplement this initial report and analysis, etc.

Statement: Mays writes, "however he omitted all of the ultrasonic cleaning steps, stating "…the ultrasonic (mechanical) steps of Figure 1 were omitted to prevent undue physical damage and complete disintegration of the Prolene fiber." [45]. Dr. Thames and his co-workers had sonicated Prolene fibers previously [41] and never saw complete disintegration of the fiber. Instead their cleaning process took off both any biological tissue and any oxidized polymer present"

RESPONSE: First and foremost, this was an intentionally oxidized exemplar fiber and no biological tissue and oxidized polymer was present. How could Dr. Mays misunderstand the explained intentions of this experiment designed to intentionally oxidize an exemplar fiber, not an explanted fiber with flesh and biological material present.

The work I referred to involved placing Prolene fibers in a Q-Lab Q-Sun Xe-3 Test Chamber. The oxidation I performed followed a prescribed ASTM procedure G155 Protocol. The UV light completely oxidized Prolene over 500 hrs. of oxidation; the time recommended by ASTM G155 procedure. This period of intense UV exposure rendered the fiber cracked and brittle, see the photomicrographs and SEM data below (Figures 31 and 32).

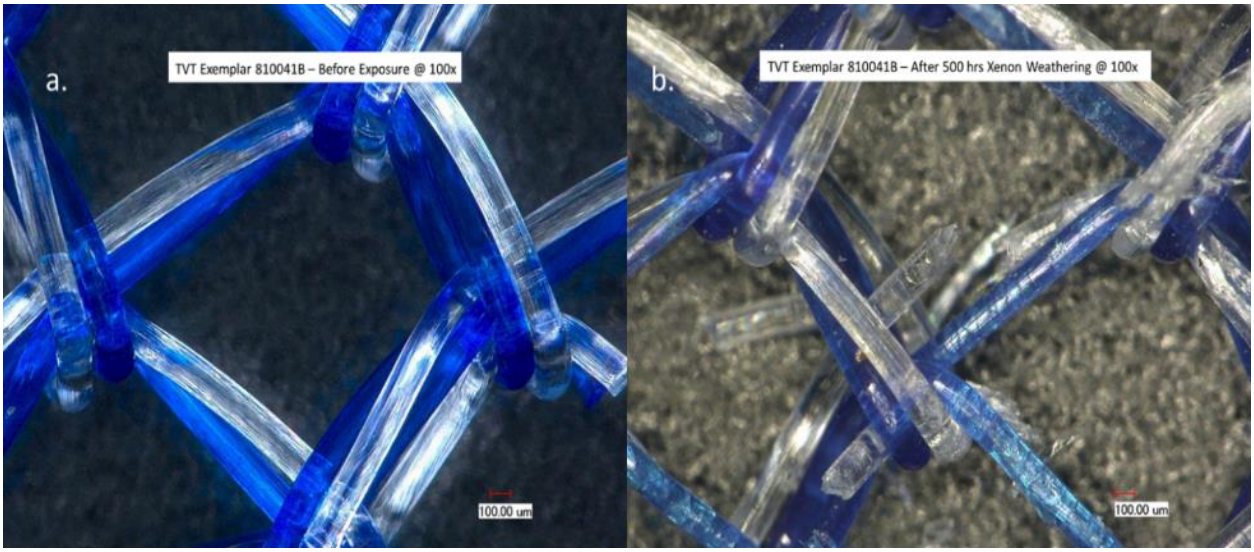


Figure 31. Light Microscopy of TVT 810041B Exemplar before UV exposure (a.) and after 500 hrs. UV exposure (b.)

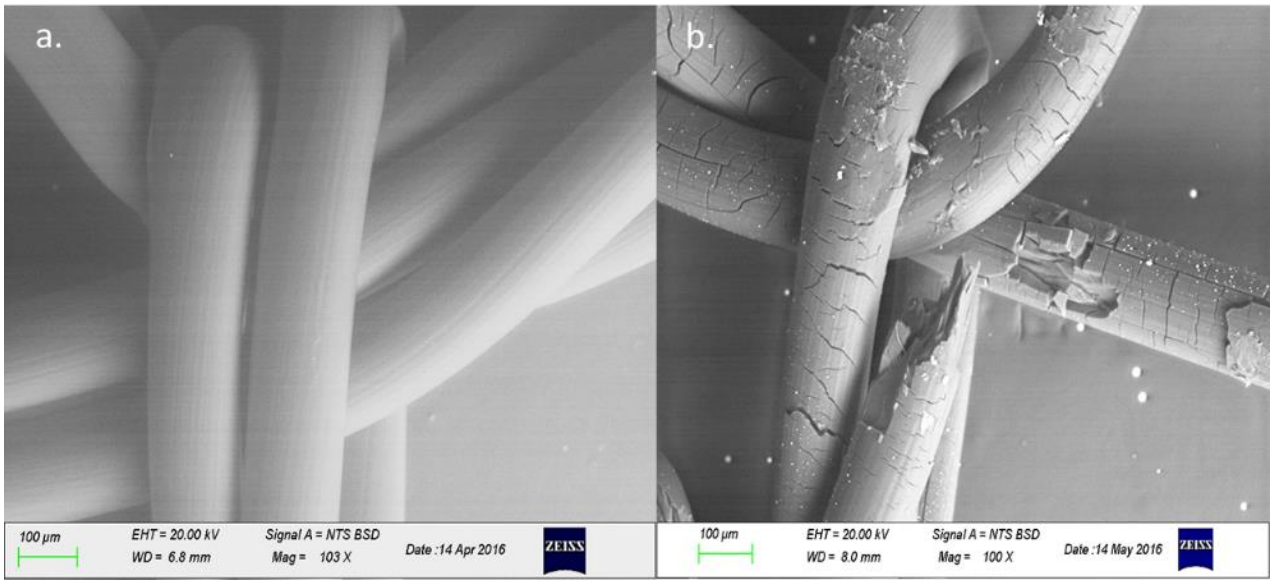


Figure 32. SEM of TVT 810041B Exemplar before UV exposure (a.) and after 500 hrs. UV exposure (b.)

Given the physical condition of the intentionally oxidized Prolene, I wrote, “Therefore, the ultrasonic (mechanical) steps of Figure 1 were omitted to prevent undue physical damage and complete disintegration of the Prolene fiber.”

A section of my September 28 Supplemental Report reads, “As previously noted herein, UV oxidation produces brittle Prolene. Thus, the ultrasonic (mechanical) steps of Figure 1 were omitted to prevent undue physical damage and complete disintegration of the Prolene fiber.” The statement is self-explanatory in that this intentional oxidation of Prolene experiment, only exemplar fiber was used and no flesh was present. Therefore, to treat already disintegrating Prolene with ultrasonics served no purpose at all and it was not done.

Statement: Even Dr. Thames now admits [45] that his 23-step cleaning protocol used in ref. 41 and his various expert reports in this case, will remove both biological tissue and oxidized polypropylene. Furthermore, he admits [45] that a bleach cleaning protocol similar to that widely used by the majority of scientists in the field, removes “the majority of the proteins”.

RESPONSE: My report of August 8, 2016 states, “To date, the cleaning protocol of Figure 1 (my 23 step process) did NOT (caps for emphasis) remove oxidized carbonyl moieties from Prolene.” Moreover, should oxidized Prolene be present it will be identified as a strong carbonyl frequency at or near 1740 cm^{-1}. There are several occasions in this report emphatically stating that carbonyl moieties, if present, will not be removed by my 23 step cleaning process. I am unable to verify Mays “carbonyl removal” statement and believe it to be in error, for that is not what occurs.

I am also unable to identify Mays statement that [Furthermore he admits [45] that a bleach cleaning protocol similar to that widely used by the majority of scientists in the field, removes “the majority of the proteins”]. I am able to confirm my statement that “Our experience has shown these first 6 steps to be those during which the majority of proteins are removed.”

Statement: Based upon all the published scientific studies discussed in this section, the step-by-step degradation process of polypropylene pelvic meshes *in vivo* may be summarized as follows: The implant causes increased activity by oxidative enzymes (foreign body response) in the vicinity of the implant. This leads to an oxidative degradation process that is evidenced by the appearance of hydroxyl and then carbonyl groups in the polypropylene, as observed by infrared spectra. There is accompanying degradation of the polypropylene molecular weight, and this process may be delayed, but not prevented, by the presence of anti-oxidants in the polypropylene. Anti-oxidants are preferentially consumed by the oxidizing species and over a period of months [25] their concentration falls below a level required to protect the polymer and oxidative degradation occurs [3]. This degradation is accompanied by a decrease in mechanical properties (embrittlement, loss of mass, decreased melting temperature, reduced compliance) of the polypropylene [3,23]. In particular, the surface and amorphous regions of the polypropylene are selectively degraded, resulting in cracks and, on longer exposure, fragmentation of the implant [22,25].

RESPONSE: It is clear Dr. Mays as a plaintiff expert, has presented his personal roadmap for Prolene’s *in vivo* oxidation. However, this roadmap to oxidized Prolene is without factual, scientific detailed data, and that is where Dr. Mays fails in his attempt to get to oxidized Prolene. Dr. Mays has failed to provide referenced real data affirming the oxidative degradation

process of Prolene and isolation of his proposed intermediary product(s) of Prolene. For instance, he has not provided hard data proving the formation and isolation of hydroxyl groups on Prolene, and finally he has not provided real data and isolation of carbonyl groups on Prolene. This issue has been discussed in detail and always with the same result; ample hypotheses from Dr. Mays but no factual, provable data, and isolated intermediary products. There is a simple answer to this query: "Prolene is not subject to scientifically significant oxidation *in vivo*."

Statement: The change in materials properties of a material implanted in the female pelvis poses unreasonable risk of harm and is defective from a design perspective in terms of the material choice made by Ethicon. A polymer that cannot maintain its physical properties in its intended application is not a suitable choice for a reasonable engineer faced with polymer choices for the intended use as a permanently implanted mesh in the pelvis, as use of polypropylene may pose an unreasonable risk of harm to a patient. This is as a direct result of the degradation of the polypropylene fibers and its effect on the performance of the mesh due to embrittlement, stiffening, and tissue reaction cascade which may each affect the polypropylene and the tissues surrounding it in vivo.

RESPONSE: Dr. Mays speaks to the issue of changing material properties posing unreasonable risk or harm, and thus he arbitrarily concludes Ethicon choice of Prolene doomed Ethicon's Prolene based materials to be defective. Once again, Dr. Mays speaks to issues for which he may be unfamiliar. Many years ago Ethicon formulated Prolene from polypropylene and five very specific additives. The composition of Prolene has remained the same of many years, and that is for a very special reason. Prolene is an exemplary polymer, known to possess enviable chemical and physical properties, making it an exemplary choice for *in vivo* implantation. For instance, Ethicon performed a 7 year dog study under the direction of Dan Burkley. This study used Prolene implanted in dogs after which on prescribed dates the animals would be euthanized and Prolene fibers would be removed for testing. Testing included the following:

- physical property determinations such tensile strength, elongation, modulus and finally toughness, and
- no significant changes in molecular weight

Such tests are fundamental for determining physical property fitness and they were collected by Dan Burkley.

- In summary, Burkley's tests of Prolene after 7 years of implantation determined that:
    - Physical property testing affirmed superior toughness of Prolene, a fine performance criteria for *in vivo* applications for its intended *in vivo* use. Physical properties actually improved with time, given fibers were plasticized by fats, and oils present in body tissue.
    - Molecular weight determinations over a 7 year period were assessed by Burkley and no significant changes in molecular weights were found,
    - The molecular weight data was bolstered by molecular weight determinations of approximately 15 plaintiffs whose testing was performed by plaintiffs' expert. Plaintiffs' expert also found no significant molecular weight losses during implantation,

- Confirmation by FTIR analysis that C=O formation did not occur in vivo
- FTIR analysis did show protein carbonyls due to the propensity of proteins to adhere to Prolene, a foreign body. Burkley did not clean his explants.
- Prolene maintains an acceptable and stable pH range
- Prolene does not meaningfully degrade in aqueous media such as flesh
- Prolene has acceptable water resistant properties

Consequently, Prolene possess excellent physical properties.

Prolene, by virtue of its chemical composition of carbon and hydrogen atoms is a hydrocarbon and therefore is not subject to scientifically significant oxidation or degradation in *in vivo* environments.

Mays references the work of Ostergard who essentially reviews biomedical publications and comments therefrom. However, since my work began with medical devices I have become increasingly disturbed by the abundance of unsupported claims and their permeation of the journal culture.

Statement; From Ostergard but included herein by Mays
" The following are relevant facts, when they were known, and where they were published, obtained from Ostergard [46].

- "1953 Any implanted device must not be physically modified by tissue fluids, be chemically inert. [46 referencing 47].

- "1986 Degradation of PP suture known as seen with SEM." [46 referencing 19]

- “1998 PP mesh shrinks 30-50% after 4 weeks”. [46 referencing 48]

- “2001 The abdominal wall stiffens after mesh insertion.” [45 referencing 49]

- “2010 Degradation occurs in all currently used meshes.” [46 referencing 24]

RESPONSE: First I would have to question if these are facts or fiction; most of what I have read recently lean more toward the fiction side rather than facts. It is alarming the number of incidents wherein some paper or someone will be quoted and immediately the material becomes fact. Certainly the 1953 statement wherein mesh products should not be modified by tissue fluids and be chemically inert should be considered. I have presented actual data from reputable sources that affirm high performance properties for Prolene as used *in vivo*. For instance, the Burkley data is reassuring in that Prolene does not meaningfully degrade *in vivo*. Moreover, its hydrocarbon backbone, its resistance to moisture effects, its toughness increase *in vivo* and its physical properties are desirable properties for *in vivo* applications. Prolene possesses such properties and they have been confirmed by scientific testing.

With respect to determining PP degradation by SEM alone, I would be very cautious given Prolene’s susceptibility for protein adsorption. In such an event, if care is not taken to insure removing proteins from the explant surface, erroneous data will result. SEM does not have the

ability to determine chemical composition. It might however be able to determine if proteins were sufficiently removed by EDS search for nitrogen; one must remember, nitrogen determinations however are variable and would likely be determined as unreliable.

Susan Lester's texts speaks to the mesh shrinkage of tissue and actually says mesh does not shrink but the tissue around it does shrink as moisture content changes from the moist to dry state. Moreover, dry tissue is prone to crack whereas moist tissue is more crack resistant.

I completely disagree with the Ostergard statement, 'Degradation occurs in all currently used meshes'-2010. The process of degradation, as defined by the medical professional may well differ from that of polymer scientists and organic chemists. In my evaluation of almost 100 explants of numerous types of Ethicon products, I did not measure oxidative degradation. Prolene is a very durable thermoplastic polymer and it exhibits those properties as an *in vivo* mesh material.

Statement: The literature clearly shows properties of polypropylene mesh change after implantation, causing adverse events like pain, scarring, and inflammation [46]. These injuries are directly caused by the change of the intended chemical and performance make-up of polypropylene mesh. Stiffening or reduced compliance of the polypropylene pelvic mesh upon degradation has important implications on the intended performance of the mesh as a biomaterial. The stiffness of a biomaterial implant must be compatible with the tissues with which it comes into permanent contact – this is fundamental to biocompatibility [50]. The mesh is designed to be soft and flexible and move with the soft pelvic tissue. However, as the polypropylene mesh undergoes oxidative degradation it becomes stiffer, much stiffer than the pelvic tissue.

Response: Literature references might be construed to "clearly show" mesh properties change after implantation to adversely affect mesh properties resulting in patient pain, yet all technically sound and collected data I have seen does not support this statement. I rely on data such as plasticization effects, where technical data can be obtained to confirm improved toughness and elasticity, as well as reduced modulus (stiffness). One therefore must question, how could a mesh material be classified as "stiff" when all chemical and polymer science principles and data says otherwise? The statement also speaks of oxidative degradation of Prolene *in vivo* as a known and accepted fact; it is not. While some may subscribe to this concept of Prolene, the first principles of polymer science and engineering do not. There are those who read the literature and statements such as, "the mesh is designed to be soft and pliable and move with the soft pelvic tissue. However, as the polypropylene mesh undergoes oxidative degradation it becomes stiffer, much stiffer than the pelvic tissue." I have read literally thousands of pages of documents and published manuscripts yet the information I have read, and the data I have collected, tells me Prolene meshes are reliable and effective performers *in vivo*.

Statement: It has been well understood for many years that polypropylene is susceptible to oxidation and it degrades by an oxidative mechanism in the body, resulting in chain scission and diminished mechanical properties (reduced compliance and brittleness). These facts are clearly documented in the peer reviewed scientific literature. Ethicon did not take into account

polypropylene's propensity for oxidation during design of its various Prolene based mesh products.

RESPONSE: It is true, PP is subject to oxidation at high temperatures, and in its formulated form as Prolene has been tested by thermo-gravimetric analysis in my laboratories.

- My reports include Thermogravimetric (TGA) data confirming oxidation/degradation of Prolene at high temperatures in the presence of oxygen. Thermal oxidation begins at 333°C or 631°F, and the process is not immediate.
- Dr. Mays is incorrect when he writes that Ethicon did not take oxidation into consideration. Ethicon formulated Prolene to contain two very effective antioxidants, Santonox R and Dilauryldithiodipropionate (DLTDP).

It is also well known that Prolene will oxidize in ultraviolet light (UV).[333] However, UV light is not a degradation issue with Prolene mesh in this matter given placement loci, and neither is high temperature. There is, to my knowledge, no acceptable and reliable scientific data confirming Prolene degradation in the body, in general, and specifically by an oxidative mechanism. Neither is there reliable data, of which I am aware, affirming Prolene's *in vivo* carbonyl groups formation, concomitant with chain scission, molecular weight loss, and loss of physical properties as Dr. Mays has declared

As an example of unreliable or misquoted data, the often referenced Liebert article of 1976 is fraught with misinterpretations[334] and is referenced by Dr. Mays as an article supporting his thesis of PP oxidation. Liebert purchased polypropylene (PP) pellets, added UV stabilizers of his choice to a portion of the PP, and extruded two PP samples for study; one was formulated with UV stabilizers and one without UV stabilizers. Note, Liebert did not use Ethicon's Prolene.

The PP fibers were implanted subcutaneously in hamsters in order to determine their *in vivo* rate of degradation. Specimens were removed periodically and analyzed by infrared spectroscopy and dynamic mechanical testing. However, FTIR is not a quantitative technique, unless FTIR absorption vs. concentration are first established and his article made no mention of this having been done. Consider also the following quote, "Although the reaction sequence is not known, several factors suggest that the *in-vivo* degradation process is similar to autoxidation which occurs in air or oxygen." Thus, in 1976 Liebert and colleagues launched an experimental program to hopefully resolve some of these issues. They began with unstabilized PP, without sufficient quantitative analytical tools, and having no knowledge of the reaction sequence they were to study. Therefore, the Liebert reaction rate data for un-stabilized PP is suspect and conclusions drawn therefrom are likewise suspect.

One Liebert quote is significant and consistent with my work, i.e. "No change in the infrared spectra or tan delta (glass transition temperature) was observed, however, for implants containing an antioxidant." Although the types of antioxidant used as well as the amounts are unknown, Liebert is emphatic that there was no change in the FTIR for stabilized PP, no carbonyl groups were produced, no aldehyde groups were produced, no peroxide groups were produced, no change in mechanical properties or infrared spectra were observed for any of the filaments containing antioxidant, etc. No change simply means no change.

Dr. Mays also speaks to the issue of Disproportionation as an accepted mechanism for PP degradation, leading to the formation of aldehydes, ketones, and carboxylic acids, with accompanying chain cleavage. Disproportionation does indeed lead to carbonyl bond formation. However, in support of his thesis of Prolene oxidation, Dr. Mays has not provided scientific reliable data confirming carbonyl formation from *in vivo* derived Ethicon explants. Neither were Liebert and others able to identify carbonyl formation with stabilized polypropylene beginning as far back as 1976. However, Liebert is often cited for supposedly confirming oxidative degradation of PP (not Prolene), and thus, the myth has continued. Ethicon does not sell nor promote PP based products without first formulating them into Prolene, i.e. PP containing five proprietary additives, two of which are highly efficient antioxidants. Ethicon's Prolene is stabilized.

Plaintiffs expert has referenced Postlethwait who implanted PP sutures in the abdominal wall muscles of rabbits and recovered specimens over intervals of 6 months to 5 years.[335]

RESPONSE: The author's conclusions are "Although in most operations these minutiae of tissue reaction concerning polypropylene are of little consequence, it may be necessary to conduct further studies to determine if they have any significance." In my opinion, no one has conducted studies showing any significance to the concept of Prolene degradation *in vivo* as there are none. We must always remember the work of Dan Burkley as his tremendously valuable work and data, proving the excellent *in vivo* stability of Prolene.[336]

Plaintiffs expert references the 1986 work of Jongebloed and Worst who examined PP surgical sutures (supplier not identified) residing in a human eye for 6.5 years.

RESPONSE: However, as noted earlier in this report, Prolene mesh is not subject to UV irradiation by virtue of its placement. It is interesting the investigators used only SEM to examine explants but did not include reference to FTIR, which would have provided helpful data for determining the explants composition and deposits thereon.

Plaintiffs expert's reference Mary once again, i.e. C. Mary, Y. Marois, M. W. King, G. LaRoche, Y. Douville, L. Martin, and R. Guidoin, "Comparison of In Vivo Behavior of Polyvinylidene Fluoride and Polypropylene Sutures Used in Vascular Surgery", ASAIO Journal, 199 (1998). Several proponents of Prolene *in vivo* degradation reference this work but seem to miss, or choose to disregard, very important scientific principles.

Mary, *et al.* used ATR-FTIR and one chose the lone infra-red frequency of 1740 cm^{-1} to confirm Prolene oxidation. The authors write in their manuscript, "both pure polymers (meaning Prolene and PVDF) are devoid of this functional group (meaning a carbonyl group)," absorbing at 1740 cm^{-1} and thus their conclusions were based on extremely meaningful, and erroneous information. Obviously they were unaware of Prolene additives and particularly DLTDP, an antioxidant with an absorption frequency of 1740 cm^{-1}. Thus, while Mary and her colleagues were unaware of the compositional makeup of Prolene they proffered opinions regarding its performance. Consequently, their lack of understanding of the chemical composition of materials they are charged with evaluating reflect poorly on their work, and any data presented or data interpretation Mary may offer is unreliable. This matter is a classic example of a peer

reviewed article possessing significant fundamental chemical errors and finding its way into scientific/medical literature. Even though, given this fundamentally grievous error, the work continues to be cited in peer reviewed articles and expert opinion reports, as it is by Dr. Mays. And, the myth continues.

Furthermore, an example of powerful and important information could have easily been obtained by securing elongation values with tensile strength data, but it was not. While tensile data was reported, elongation values were non-existent therefore important polymer toughness values could not be determined.

Aside from the erroneous FTIR data, Mary also used a rigorous preparation and cleaning protocol for the SEM samples in that they were:

- Fixed in glutaraldehyde solution, rinsed in distilled water, and post fixed with osmium tetroxide.
- Drying was affected by immersion in ethyl alcohol solutions, followed by critical point (-70°C) using below freezing liquid carbon dioxide (this process alone would almost certainly generate significant artifacts, i.e. cracking).
- Specimens were coated with sputtered gold palladium and viewed by SEM.
- This "fixation" and "drying" process is very rigorous and would produce a brittle material especially during the carbon dioxide critical point drying process. Any movement of the sample would shatter or break surface materials causing "cracks." Yet they speak to the issue of viewed cracks and presumably subscribe them to mesh deficiencies, giving no consideration to the very high probability of sample preparation artifacts nor the fixation processes employed.
- Mary and colleagues base their opinions in part on Liebert, stating he found PP oxidation to carbonyl groups, chain scission, and oxidation within a few days after implanting in rats. What these authors do not say is extremely important to the scientific community; that is, Liebert used PP without UV absorbers and antioxidants, but when UV absorbers were part of the PP formulation, no Prolene degradation of any kind was noted. Such omissions of critical data serve to continue propagation of misinformation to the scientific community via the peer review process.
- Neither have plaintiffs' experts made these important scientific facts known, but simply continue to reference the flawed Mary work as we see in the present instance.
- Costello, in a similar fashion, continues to be referenced in peer review manuscripts yet he and colleagues gave no consideration to tissue "fixation in formalin." "Fixation" is a chemical crosslinking reaction between formaldehyde and proteins, and typically takes place in the surgery suite when the surgeon explants mesh and places the explanted flesh into a formalin solution. The fixation reaction continues for an extended period while immersed in formalin. The fixation product is a rigid, hard, insoluble, porous, and brittle; the chemistry of "Fixation" was described more than 50 years ago, and is thoroughly discussed in the chemical literature, and used extensively in medicine for more than 50 years. For instance, see Dr. Susan Lester's Manual of Surgical Pathology is an excellent reference.[337] The manual is a treatise said to be in most surgical suites in North America. Dr. Lester discusses fixation thoroughly, and several of her topics deal

specifically with issues in this litigation. However, I have not seen her Manual of Surgical Pathology in Dr. Mays bibliography.

- "Fixation in Formalin" simply cannot be ignored. The Formaldehyde-Protein polymer formed during the fixation process must be removed from explants prior to their testing.

- Those who ignore this well know, established, chemical and polymer science precept cannot hope to understand the magnitude of its influence.

- Bracco, in the peer reviewed manuscript, titled Comparison of Polypropylene and Polyethylene terephthalate (Dacron) meshes for abdominal wall hernia repair: a Chemical and Morphological Study state "For the first time, by scanning electron microscopy (SEM), polypropylene (PP) excised meshes (ethylene oxide sterilized) for abdominal wall hernia repair have been shown to be greatly damaged physically,…." The PP or PET mesh explants were fixed in 4% formalin. Bracco writes "in order to eliminate any organic residue, the fragments were treated for 24 h with sodium hypochlorite solution (Fluke 6-14% active chlorine) at 37 ^{o}C and washed with distilled water. These fragments were extracted for 24 h with boiling cyclohexane. The extracting cyclohexane was removed with a rotating evaporator and the residue recovered in a few drops of hexane." At this point in the Bracco study, explanted mesh has been fixed in formalin, and extracted with cyclohexane. Thus the "Formaldehyde Fixation" process has been performed and the hard, brittle, insoluble, composite formaldehyde-protein polymer has formed. It is not removed by cyclohexane due to its insolubility in this non-polar, hydrocarbon solvent. To further complicate SEM analyses, the samples were sputter coated with gold "in preparation for SEM analysis." Removing the cyclohexane soluble materials would remove long chain fatty acids, esters, and other organic soluble materials functioning as plasticizing agents. Thus, their experimental approach will adversely affect Prolene's physical properties.

- The sample having been prepared for SEM analysis is at this stage, without plasticizing agents, encased in a formaldehyde-protein composite polymer and made even more rigid by sputter coating in gold. This PP material can be viewed in Bracco, Fig.2 and Fig. 3. The explant mesh manufacturers were not identified but all 25 mesh samples were from different manufacturers. Two SEM images of PP were taken as representative of all other PP excised mesh fragments. Moreover, this study did not consider any formulation differences in the PP mesh product, nor any difference in properties formulation differences would produce.

- The explants were insufficiently cleaned, i.e. soaking in sodium hypochlorite solution for 2 hours at 37 ^{o}C followed by rinsing with distilled water is an insufficient cleaning protocol for explanted mesh.

"In all PP excised mesh fragments listed in Table 1 independent of the manufacturer or the implantation time, the filaments appear badly damaged (Fig. 33). This seems to be in disagreement with what is clinically observed [11, 12], namely that PP meshes give an inflammatory response and an extraneous body reaction less than the PET ones." Bracco, like

many others, has, for whatever reason, given no consideration to formalin fixation and the resulting formalin-protein polymer. The strongly adhered proteins, and their subsequent reaction with formaldehyde readily accounts for the images of Fig. 34 and 35 taken from Clave. This represents yet another peer reviewed article that did not properly consider the chemistry, and its effects, of the Formalin Fixation process.

The photomicrograph in Costello's Figure 5 is precisely what one would expect of an improperly cleaned explant. Bracco makes specific reference to his Figures 3 when postulating a primary cause of the cracked and degraded morphology was absorption of small organic molecules of biological origin. Even Dr. Mays was in disagreement with Bracco and his statements which disregarded the plasticizing effects of lipids.

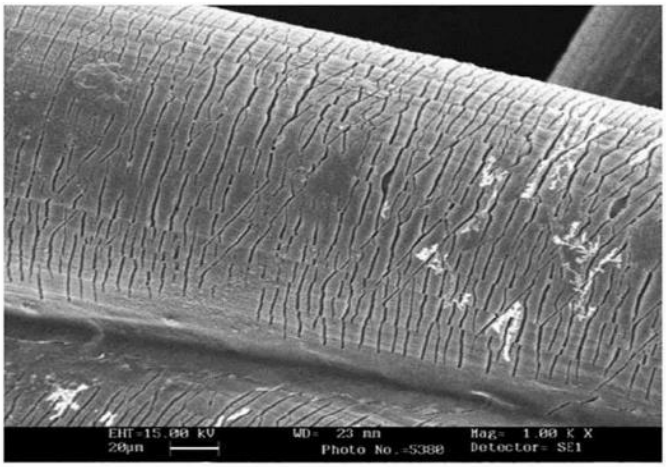


Fig. 3 Scanning electron microscopy (SEM) micrograph (1,000×) of fragment #9 polypropylene (PP)

Figure 33: SEM Image of explanted PP fiber from Bracco's Figure 3 [33][338]

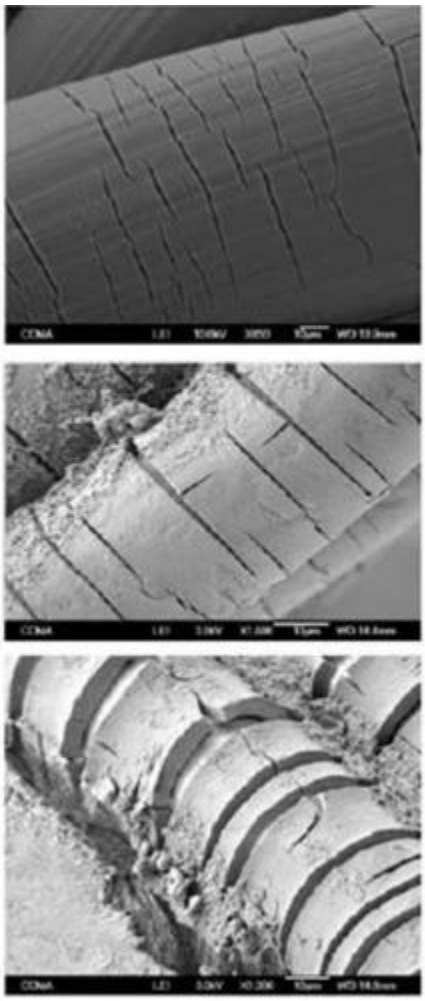


Figure 34. SEM of Transverse Cracking in Explanted PP Fibers from Clave (Figure 4) [Ref. 24][339]

Figure 34 is plaintiff's expert reference to Clave, *et al.* who reported PP mesh damage as "superficial degradation." Figures 1 and 2 are classical for explanted mesh with essentially no protein removal from PP fiber(s). It is a simple matter to perform an FTIR analysis on samples similar to shown in Figures 1 and 2 to confirm the proteinaceous nature of the protective sheath formed around the PP fiber. We have done so in our labs and, of course, confirmed the composite sheath is of proteinaceous composition, not PP. Plaintiffs have apparently not taken the advantage of an FTIR of material shown in Figure 34. The proteinaceous composite is formed during the fixation process in formalin.

Plaintiffs expert, Costello, Bracco, Mary, LeFranc, Clave, and others are literature contributors who have, and perhaps unknowingly, become part of the misinformation world of PP mesh and its *in vivo* performance. None seem to have recognized and/or appreciate the significance of fiber or mesh "Fixation in Formalin." Consider now LeFranc who included Clave's photomicrograph (Figure 25.9) of "Degraded PP Mesh." It is obvious, even to one not skilled in the art, material(s) possessing surface cracks of the order of magnitude as shown in Clave's

Fig. 25.9 would expect massive cracking via crack propagation through the fiber to ultimate fiber rupture, and total loss of mechanical properties (Figure 35).

Fig. 25.9 SEM observation of degraded PP mesh under septic environment

Figure 35. Clave Figure 25.9[340]

However, Plaintiffs expert has written "It is likely that an increase in free volume of the amorphous regions of implanted PP fibers due to plasticization from the absorption of small, biological organic molecules facilitates increased penetration into the PP fibers by oxygen and other oxidizing chemical species, thus accelerating PP fiber degradation due to oxidation." This is speculation without scientific foundation and apparently crack propagation is unknown to Dr. Mays.

Plaintiff expert references his work with the publication "In Vivo oxidative degradation of polypropylene mesh." I question the statement "It is now well-known that strong oxidizing agents such as hypochlorous acid and hydrogen peroxide are generated as byproducts of the inflammatory response of the body to an implant, and these agents can degrade and embrittle polypropylene, with a loss of flexibility due to oxidation selectively removing the less dense amorphous regions of the material." It is the underscored portion for which I have seen no credible, conclusive scientific data to confirm "these agents can degrade and embrittle polypropylene, with a loss of flexibility due to oxidation,---." This is pure speculation with no data. Moreover, Bracco has shown he does not understand the concept of "plasticization" and the resulting increase in toughness of plasticized Prolene.[341]

Imel and Mays, using Boston Scientific mesh, published their work with the intent to "test whether or not oxidative degradation is responsible for observed changes in the mesh upon implantation." They chose analytical tools such as FTIR, SEM, TGA, GPC, and TEM by which

to collect data. However, only 4 of 11 samples "were cleaned of residual biological material by soaking 24 h at room temperature in sodium hypochlorite solution (7.85% available chlorine), followed by rinsing extensively with water and drying in a vacuum oven at room temperature." This cleaning technique is insufficient to insure all "fixed proteins" are removed from the Boston Scientific Explants, thus casting doubt and speculation on data collection and opinions therefrom. Moreover, cleaning was only attempted with 4 of 11 samples.

Furthermore, their data display is inferior, particularly with respect to FTIR. The authors write "Clear signs of oxidation are seen in the FTIR spectra of all four implants as evidenced by broad peaks centered around 3400 cm^{-1} (hydroxyl and peroxide) and between 1700 and 1750 cm^{-1} (this is the carbonyl region where some antioxidants absorbs)." Moreover, there are no instrument derived frequency displays for the spectra, and thus absorption assignments are in doubt.

The TGA data of Fig. 3, page 133, shows the most thermally stable samples tested to begin weight loss at less than 300°C (samples of Fig. 3A) and less than 250°C for Fig. 3B. Weight loss for Prolene begins at approximately 333°C, thus their data does not apply to Ethicon's Prolene.

SEM data and assignments are suspect and misleading given sample preparation, SEM photomicrographs, and data conclusions. Consider the following from the Imel, Mays article;

1. "However, SEM and EDS was performed on all 11 samples."
2. "The explanted samples were contained in jars of formalin solution." This confirmed explant fixation in Formalin.
3. Explanted samples were rinsed in ultrapure (deionized) water and then allowed to air dry. After drying, the explanted samples were mounted on aluminum SEM sample holders with double sided, conductive tape.
4. "In the preparation for SEM testing sample XP-11 and only ONE sample (XP-11) was treated with sodium hypochlorite solution for removal of biological tissue using the published procedure of Bracco" (See Fig.4, sample C)

Given these data and SEM photomicrographs of the report it is obvious explant samples were not cleaned or far from being properly/thoroughly cleaned of the formaldehyde fixed proteins/flesh remained on the explants. For instance, formalin fixed flesh can easily be seen in Fig.4, C, D, E, and F; Figure 5, A, B; Fig. 6, A, B, C and D; Fig. 7, A, D, E, and F.

The authors set out to use EDS data for the following purpose, "EDS was used to look for the presence of oxygen in polypropylene fibers, which would indicate that degradation due to oxidation has occurred." It is clear the authors do not realize oxygen and nitrogen containing tissue remains on the explants as they were not sufficiently cleaned after fiber fixation, or they wished to ignore its presence. Viewing Fig.1, A is a Pinnacle Control while B is an Obtryx Exemplar control and in the lower section of Fig. 1 EDS spectra, E and F, are controls, yet they show the presence of Carbon and Oxygen. Surely the controls are not oxidized, and that EDS data for both show presence of Oxygen defeats their thesis for confirming oxidative degradation by EDS. The SEM photomicrographs confirms residual flesh, and given all samples were fixed in formalin, all explants are expected to possess, at the very least, Carbon, Hydrogen, Oxygen

and Nitrogen. Nitrogen, however, is difficult to analyze by EDS and there may be times when Nitrogen is present but it is not shown on a corresponding EDS spectra.

The GPC data is likewise suspect given the authors did not consider small molecule absorption. Any absorbed, low molecular weight materials would be eluted through the GPC column, as would higher molecular weight polymer fractions, and in so doing impact the molecular weight data. Bracco clearly confirmed the presence of low molecular weight chemicals via his extraction/FTIR technique.[342]

Plaintiffs expert cites Ostergard, who has reviewed medical literature, and formed conclusions not based on fact, but unsubstantiated data that found its way into the medical literature, like that of Liebert for example.[343] Medical professionals were not attuned to the effects of the fixation process, and it was not considered in many, many instances.

Plaintiffs expert responded to work of Dr. Peter Moy of Ethicon in the following way:

> In 1985, a series of experiments, including FTIR, TEM, and histology, were performed to determine the clinical functionality of cracked sutures, the cracking mechanism, and effects of anti-oxidant concentration.[344] Dr. Moy noted that laboratory experiments had not replicated the cracking observed in explants, and proposed a systematic evaluation of explanted Prolene sutures.
>
> **Response**: Laboratory experiments do not replicate those from the body, as body tissue is not present for formalin fixation. It is clear that Moy and others had not fully realized the significance of the formalin-protein fixation reaction, as would be the case with an explant but not with a lab originated experiment. Dr. Moy was correct in suggesting a systematic evaluation of explanted Prolene sutures.

Plaintiffs expert states, “Ethicon was also informed of the risks inherent to using polypropylene in an implantable medical device through the Material Safety Data Sheet (MSDS), which states that polypropylene is incompatible with strong oxidizers.”[345] We have shown that not to be the case, as our earlier cleaning protocol, in the Lewis and Batiste matters, used nitric acid as one of the cleaning agents and no oxidation was noted. It is quite clear, therefore, Prolene is not easily oxidized given these and other data.

In an effort to illuminate meaningful data on a cleaning protocol I have developed in concert with Dr. Kevin Ong, I am including my report “Intentional Oxidation of Prolene Mesh.” This supplemental data focuses on the viability of my cleaning protocol for Prolene mesh explants. There are those, especially Mays, who are critical of my cleaning process. Therefore, this report will show the method of cleaning developed is appropriate, safe, and sufficiently mild in every way such that cleaning does not affect Prolene’s surface in any way.

Response to the Dr. Duane Priddy Report

Plaintiff's expert pens the statement, "PP is not inert, and must be heavily stabilized with the addition of antioxidants in order to simply survive." which is misleading. Moreover, when plaintiff's expert performed GC-MS analyses of Prolene he found only one of 5 additives, Santonox R, thereby confirm the inferiority of his analytical technique or equipment or both

For instance, Plaintiffs expert writes, "My testing in this case (gas chromatography – mass spectroscopy (GC-MS)) did not detect the presence of any of the additive other than Santonox R.[346]

- Prolene's formulation contains 5 additives.
- This disclosure by Plaintiffs expert in question any and all analytical data he has obtained, and I will respond to several of my concerns herein. It is particularly troubling in that he uses the data collected for his opinions as stated herein with respect to *in vivo* efficacy of Prolene.
- He references essentially all articles to which I have responded in this and other reports concerning this litigation, and for this reason I will not respond separately to each one.
- He, like others, reference and show SEM photomicrographs of protein-containing explants and believe them to be oxidized Prolene.

Plaintiff's expert provides a list of environmental conditions where he states it is impossible for Prolene to exist, such as:

1) high surface area exposed to oxygenated medium,
2) is under stress,
3) is in a constant warm environment, and
4) is exposed to fluids containing organics capable of extracting antioxidant stabilizers from the exposed surface.

Plaintiff's expert dismisses, however, the more than 60 successful years of Prolene suture history embodying each of his "impossible for Prolene to exist statements." He also fails to provide scientific references supporting his beliefs.

Plaintiff's expert praises and utilized two ASTM procedures for his Prolene "evaluation" and they are ASTM D3895 "Oxidative Induction Time" testing, and ASTM 1980-02, "A Standard Guide for Accelerated Aging of Sterile Medical Device Packages." Presumably he uses data from these ASTM methods from which to formulate his opinions herein. In reading the procedures, one finds the following statements taken from these ASTM methods section. I have included my response to each of the following in italics.

- The OIT is a qualitative assessment of the level (or degree) of stabilization of the material tested. *Thus, as a qualitative test no lifetime predictions, if asserted, would be reliable.*
- The OIT measurement is an accelerated thermal-aging test and as such can be misleading. *This caution alone is sufficient for the serious scientist to seek other, more reliable methods of testing. Consideration must be given the "Transition State" and "Energy of Activation" required for chemical reactions to proceed.*

- There is no accepted sampling procedure, nor have any definitive relationships been established for comparing OIT values on field samples to those on unused products, hence the use of such values for determining life expectancy is uncertain and subjective. *This warning alone disqualifies use of these ASTM procedures for the matters at hand.*
- Volatile antioxidants may generate poor OIT results even though they may perform adequately at the intended use temperature of the finished product. *Yet, another warning not often considered, but critical. Volatile materials, at temperatures of testing, can escape the substrate rapidly and provide erroneous data.*

- This guide provides information for developing accelerated aging protocols to rapidly determine the effects, if any, due to the passage of time and environmental effects on the sterile integrity of packages and the physical properties of their component packaging materials. *These tests are designed for evaluating packaging materials, not biomaterials to be used in vivo.*

- Real-time aging protocols are not addressed in this guide; however, it is essential that real-time aging studies be performed to confirm the accelerated aging test results using the same methods of evaluation. *These test requirements have NOT been met by Plaintiffs expert.*

- To ensure that accelerated aging studies do truly represent real time effects, real time aging studies must be conducted in parallel to accelerated studies. Real time studies must be carried out to the claimed shelf life of the product. *These test requirements have NOT been met by Plaintiffs expert.*

- Accelerated aging techniques are based on the assumption that the chemical reactions involved in the deterioration of materials follow the Arrhenius reaction rate function. *Plaintiff's expert does not address this matter, thereby he cannot offer assurances for the quality of his data.*

- Care must be taken not to elevate aging temperatures solely for the shortest possible accelerated aging time. Excessively high temperatures may have an effect on the material that may never occur during real time or at room temperature (see Appendix X1). *The effect of elevated temperature on the transition state for this reaction to occur is unknown, and thus the test is completely unreliable.* Guidelines for selecting an aging temperature are as follows:

    1. Accelerated Aging Temperature (T_{AA}) should be below any material transitions or below where the package distorts. Consider the thermal transitions of the materials under investigation, for example, the choice of T_{AA} should be at least 10°C less than Tag. *The T_m of Prolene is 162°C with an ASTM requirement of 10°C less than T_m. Thus, the testing temperature should be no more than 152°*

C, yet Plaintiffs expert conducted his experiments at 200 °C, well out of the acceptable range of this ASTM procedure by 50°C.

2. Keep T_{AA} at or below 60°C unless a higher temperature has been demonstrated to be appropriate. Temperatures higher than 60°C are not recommended due to the higher probability in many polymeric systems to experience nonlinear changes, such as percent crystallinity, formation of free radicals, and peroxide degradation. *The test temperature of 200 °C does not meet this ASTM requirement.*
3. However, like all accelerated aging techniques, it must be confirmed by real time aging data. *Plaintiff's expert report is devoid of this requirement.*

- Packages and materials that have been subjected to aging, that is, accelerated and real time, must be evaluated for physical properties and integrity. *There is no evidence Plaintiffs expert accomplished this testing requirement, see immediately below.*
- Some of the physical strength properties to be considered for selection are flexure, puncture, tensile and elongation, tear, impact resistance, abrasion resistance, yellowness index, microbial barrier (Test Method F 1608), seal strength (Test Method F 88), and burst strength (Test Methods F 1140)
- If the real-time aging results meet the acceptance criteria, then the package's shelf-life is validated. *Real time aging results have not been presented by Plaintiff's Expert and thus this testing protocol does not validate Plaintiffs expert data.*
- If the real-time aging results fail to meet the acceptance criteria, the shelf-life must be reduced to the longest shelf life for which real time testing has been successful. If product has been released to the market at risk based on the accelerated aging data, a careful review must be performed and documented, and the appropriate action taken.
- The author states, "Because of its (Prolene) poor oxidative stability, PP is generally used primarily to manufacture products that have a short service life.[347] *This statement is unfounded, has no technical support or merit. My laboratory data confirms Prolene an initial thermal degradation temperature for Prolene begins at approximately 333 °C*.
- Plaintiff's expert makes a sweeping statement that, "For example, when plastics are placed in the body, they are exposed to organic liquids (e.g., blood and fatty oils called lipids, glycerides). These chemicals act to extract the antioxidant stabilizers (very small molecules) from the long polymer chains in the plastic." *The work of Dan Burkley in his 7 year dog study proved this statement to be in error. After 7 years, physical properties of explanted sutures were significantly tougher than when implanted. Thus, physical properties of Prolene improved, rather than declined as the author would lead you to believe.*

Plaintiff's expert provides a partial chemical structure explanation of the possible free radical reactions of Prolene. And, Of course, Ethicon's antioxidants effectively retard these reactions. In attempts to explain the reactions he suggests to those, who are obviously not knowledgeable in chemistry, that the degradation reaction occurs at will, essentially with little to no inhibition.

However, nothing could be farther from actual facts. Consider for instance the well-known concept of the Transition State Theory. It is known that in order for a chemical reaction to proceed, the activation energy for formation of the initiating activated species (the free radical) must be achieved[348] before any oxidative reaction can occur. Plaintiffs expert has not considered this mechanistic requirement, and until that is properly done, all comments and statements attributed to Plaintiffs expert regarding Prolene degradation is sheer supposition and not supported by basic chemical principles.

Section VII of Plaintiffs expert report is quite telling and deserves considerable attention. This section begins with the statement,

> "The PP used in Ethicon mesh is stabilized using antioxidants (e.g., Santonox R). Ethicon documentation reveals that there are additional additives added to the Prolene resin, including Calcium Stearate, Dilaurylthiodipropionate (DLTDP), Procol LA-10, and CPC Pigment 22. My testing in this case (gas chromatography – mass spectroscopy (GC-MS)) did not detect the presence of any of the additive other than Santonox R."

First, in setting the record correctly, Prolene is formed only after all five required additives are added to PP and properly extruded. Thus, Prolene, in fact, does contain ingredients the author says his testing could not identify. It is obvious therefore, that Plaintiffs expert has offered incorrect opinions based on erroneous data.

Plaintiff's expert offers Figure 1, a SEM photomicrograph taken from Henri Clavé, as have others to which I have responded.[349]

Plaintiff's expert Summary and conclusions are not supported by existing, high quality science. Likewise, plaintiffs' expert continues to discuss PP (polypropylene) rather than Prolene. I have responded to his summary and conclusions in italics, i.e.

- He states, "In order to fabricate a mesh, the PP polymer chains must be short." *The term "short" is not a term of art when discussing polymer science. It is a relative term and has no significant meaning herein.*
- He states, "PP mesh will rapidly lose its strength as the polymer chains disentangle when the mesh is placed under mechanical stress." *Tensile strength, elongation and modulus values for Prolene establish the polymer as a high performance thermoplastic.*
- He states, "The PP is inherently oxidatively unstable compared with other plastics (because of the tertiary bonded hydrogen) forcing the addition of high levels of antioxidant stabilizers to be added to the PP to allow it to be stable enough to be fabricated into mesh without material degradation." *His statement defies reality given the annual product in the U.S. is approximately 8.4 million metric tons, and 52.2 metric tons worldwide.*
- He states, "The antioxidants are depleted by migration from the mesh and by oxidation as they do their job to protect the PP against degradation." *Plaintiff's expert has not provided reliable information to affirm his belief. Ethicon's Dan Burkley managed a long-*

term scientific study and collected laboratory data confirming exemplary antioxidant protection provided by Santonox R and DLTDP to Prolene during a 7 year in vivo period. Prolene's physical properties did not diminish over the 7 year period, but instead improved dramatically.

- He states, "Oxygenated liquids (e.g., blood, lipids and glycerides) present in body tissue extract antioxidants from the surface of PP allowing rapid degradation and embrittlement of the surface of the mesh fibers*." Plaintiff expert again offers no quantifiable data to his claims, and does not consider the Burkley study. His writings are in strict contradiction to Prolene's performance.*
- Plaintiff's expert refers to the work of Dr. Jimmy Mays, yet he did not mention or is unaware that Dr. Mays did not use Ethicon's Prolene, but a Boston Scientific product.
- Plaintiff's expert's Section X includes "the essence of any accelerated aging methodology begins with an understanding of the stresses applied to the polymer during service, and how those stresses may affect aging properties." He continues by writing, "Some typical polymeric stressors include thermal, oxidative, chemical, and physical stresses." *Surely he understands his teachings defeat his data collected according to ASTM tests F1980 and D-3895. Plaintiff's expert analytical techniques require 200 $^{\circ}$C (392 ^{o} F). He has not, however, given an explanation as to how this greatly elevated temperature may affect aging properties of Prolene.*
- Plaintiff's expert speaks of embrittlement of Prolene. *He has offered no scientific data to affirm this precept, and neither has he suggested how to measure or test for embrittlement.*
- Plaintiffs expert states, "Therefore the OIT data is a <u>best case</u> situation because the only mechanism for loss of antioxidant during the OIT tests is chemical reaction; i.e., loss by migration into body fluids is not taken into account." *Plaintiff's expert completely dismisses loss by excessive heating, a stressor he has identified*.
- Plaintiff's expert refers to liquid chromatography data supposedly confirming the gradual decrease in Oxygen Induction Time as being due to migration of antioxidant to the surrounding medium. *Plaintiff's expert could only detect one of five known Prolene additives via his GC-MS technique. He also fails to include the following comments from the authors of work cited[350] i.e. "The large scatter in the data makes an accurate assessment of the activation energy impossible" and "The low boundary loss rate makes the assessment of the antioxidant diffusivity far from ideal and it is associated with a sizeable uncertainty." In other words, the authors of the cited article candidly reveal their technique is not quantitative nor precise-yet this is a technique Plaintiffs expert has cited and used for data collection in this matter. <u>Note the authors of the cited article state -the activation energy of the Transition State Theory cannot be accurately assessed by their methods</u>.*

Section XI of Plaintiff expert report discusses data collection from 10 Ethicon mesh samples extracted with methylene chloride and analyzed by GC-MS to identify and quantify the relative amount of Santonox R present in the mesh samples. *If the GC-MS spectroscopy technique and/or instrumentation used by Plaintiffs expert could identify only one of five Prolene formulation additives, little to no confidence can be attributed to his data.*

Plaintiff's expert report **Section XII** includes discussion of explants provided by Dr. Robert Guidoin to Ethicon employees. First and foremost, the explants were evaluated in their "as is" state. While there is suggestion that some of the explants may have been subjected to a bleach treatment, it is Dr. Guidoin[351] who coauthored a manuscript on the difficulty in cleaning explants, more often than not requiring strong chemicals.

Plaintiff's expert **Section XIII. Expert Opinion** includes lack of reliable data and unsupported opinions to which I am in total disagreement. None of his opinions are supported in any way by reliable and believable scientific data. Consider as one example the following:
Priddy – Oxygen Induction Time Data for Gynemesh Explants

	OIT-MINUTES	ISOT-MINUTES
Sample 1.	42.4	35.0
Sample 2.	38.4	34.0
Sample 3.	32.6	21.0
Sample 4.	23.2	19.2
Sample 5	18.6	16.4
Sample 6	31.8	29.00

These data are in conjunction with his writings, "that Over 150% variance was found between the 10 exemplar samples," while his reported data for Gynemesh exemplars showed greater than 100% variance. Whether you take the exemplar or explant data, it is very clear that the test methods he has employed lack the sophistication to provide meaningful values from which one can draw valid conclusions.

Response to the Dr. Scott Guelcher Report

Guelcher Summary of Opinions followed by Response

1) Polypropylene (PP) reacts with molecular oxygen by autoxidation outside the body at elevated temperatures, resulting in chain scission and deterioration in its mechanical properties.

Response: Of course, however our analytical work has confirmed thermal degradation for Prolene in an oxygen atmosphere begins at approximately 333 °C.

2) After implantation in the body, polypropylene reacts with reactive oxygen species secreted by inflammatory cells, resulting in oxidation, chain scission and mesh embrittlement.

Response: Liebert, who is cited by Guelcher, estimated the induction time for PP oxidation under *in vivo* conditions (37^{o} C in 3.3% O_2) is approximately 20 years. He followed with data that did not support his opinion. His opinions were dependent upon carbonyl group formation and positive proof of PP oxidation. However, PP oxidation hasn't been proven since no carbonyl groups have been clearly identified. Furthermore, oxidation, as alleged by Guelcher, results in chain scission, molecular weight loss, and loss of toughness. None of these properties have been confirmed. In fact, the work of Burkley showed that Prolene was tougher after 7 years of implantation then the day it was implanted and no significant weight loss was noted.

3) The dynamic environment where the polypropylene mesh is implanted coupled with the foreign body reaction leads to oxidation, chain scission, reduction in molecular weight, embrittlement, degradation, flaking, pitting, and cracking.

Response: Oxidation produces Carbonyl Index and there is no proof this has occurred. Fayolle[352] and particularly George Wypych[353] show that, loss of molecular weight cannot occur without carbonyl group formation.

4) The human body does not stop responding to an implanted mesh, or any frayed particles of mesh released during implantation, unless the product is removed in its entirety;

Response: Significant data exists proving proteins rush to the surface when a foreign body is implanted.[354,355,356] The proteins (Collagen) immediately adsorb strongly to PP and, as such, are difficult to remove, as others agree.[357] We have shown this by our own experiments. See Appendix R1 (SEM, FTIR, LM).[358] The adsorbed protein layer coats the explant surface and "protects" it such that other body cells do not "see" PP as a foreign object, they only "see" adsorbed proteins.

5) The mesh devices examined for this report are intended to last for the lifetime of the patient, but the presence of antioxidants does not permanently protect the PP against degradation, and thus it is not possible to guarantee that it will perform its intended function after implantation;

Response: I have not seen data proving implanted Prolene will degrade to the extent its intended function is compromised during an implantee's lifetime. To the contrary, our work has confirmed no degradation of Prolene explants.

6) The effects of oxidation on the stability of Prolene were known to Ethicon prior to launching its SUI and POP devices, but the company did not consider the risks associated with polypropylene oxidation on the stability of Prolene mesh, to the detriment of patients implanted with the devices;

Response: Ethicon had, since the 1960's, many years of profound *in vivo* performance, and thus a successful history of Prolene sutures "implanted" for a "lifetime."

7) Polypropylene mesh is not inert and its properties change after implantation, which can lead to adverse events in an implantee; the use of heavy-weight meshes directly correlates with more exposure of polypropylene to the Foreign Body Reaction and greater changes after implantation, which increases the risk of complications.

Response: I have stated that I know of no totally inert material. However, I have also stated that properties of Prolene, given it intended use in the human body, are not compromised to the extent its performance properties are affected.

The **BACKGROUND** section of Dr. Guelcher's report speaks to some mesh materials components yet omits other very important ones such as, Procol LA and Calcium Stearate. These formula ingredients have precise functions and are thus important to Prolene's performance. Consequently, opinions from anyone offering conclusions about Prolene performance, and is unaware of these materials and their function, is suspect.

DISCUSSION

Section 1, Polypropylene reacts with molecular oxygen outside the body by the process of autoxidation.

It should be noted that Plaintiff's expert has devoted this section to PP and oxygen reactions at high temperatures outside the body.

The accepted mechanism of PP oxidation, as presented (Figure 1), results in carbonyl moiety formation, i.e. a ketone, and confirms PP chain cleavage or scission followed by molecular weight loss. Chain cleavage breaks bonds between carbon atoms, and divides PP at the site of bond cleavage into two distinct polymer units of lower molecular weight, one of which possesses a carbonyl bond (C=O). Thus, the two concurrent processes are inextricably interwoven, as you cannot have chain cleavage without carbonyl bond formation. This is a very important concept as plaintiffs repeatedly speak to the issue of autoxidation (which, if it occurs does so by chain cleavage and carbonyl bond formation). However, their expert tested more than 20 explants by GPC analyses, as did Dan Burkley of Ethicon during his 7-year dog study, and found NO significant molecular weight loss[359]. One simply cannot have it both ways; if oxidation occurred in the twenty odd explantees of plaintiff's expert report or in the 7 year dog study of Dan Burkley, there would have been molecular weight loss sufficient to produce property degradation, and loss in toughness; there was no scientifically significant measurement of either.

Much of the data plaintiff expert presents is devoted to polypropylene (PP), and not Prolene. By Plaintiffs expert's writings he fully understands Prolene is not PP but, a formulated product of more than 50 year service as Ethicon sutures. Consequently, his report is misleading to the non-scientist unfamiliar with differences in PP and Prolene. For instance, in his Discussion section the first heading (1) begins with "Polypropylene with reacts with…", and in the second heading (2) we see "After implantation in the body, Polypropylene reacts with reactive oxygen…."

Section 2, After implantation in the body, polypropylene reacts with reactive oxygen species secreted by inflammatory cells, resulting in oxidation, chain scission and mesh embrittlement.

Plaintiff's expert discusses topics playing no part in the current matter, i.e. unstabilized polypropylene in oxygen and stabilized polypropylene in 100% oxygen at elevated temperatures of 120 and 140^{o}C.

Moreover, the 1965 Oswald and Turi reference states "most of these experiments were performed on unstabilized polymer (meaning polypropylene only and none of the specialized additives found in Prolene)."

Plaintiff's expert quotes "Liebert, *et al.* (1976) reported the oxidation of unstabilized PP filaments…" For instance, Figures 3 and 4 of the report are titled "Degradation of unstabilized PP" and "Stability of unstabilized PP at room temperature," respectively. On the one hand while he reports the oxidation of unstabilized PP plaintiff's expert essentially dismisses Liebert's induction time estimate for oxidation under *in vivo* conditions to be approximately 20 years. In fact, the entire reference segment on page 6 of his report deals with Polypropylene (PP) not Prolene. The Fayolle[360] reference uses unstabilized PP (not Prolene) while discussing "molecular weight decreases with time when exposed to oxygen at elevated temperatures." Again, Prolene is not the subject of their investigation which is carried out *in vitro*, in oxygen, and at elevated temperatures (90 $^{\circ}$C).[361] These are conditions to which Prolene *in vivo* would never be subjected, and thus are totally inappropriate for consideration in this matter.

To further confuse the matter at hand, plaintiff's expert speaks to a "a morphological progression of the foreign body reaction on a poly(ether urethane),"[362] a polymer type, and thus chemical structure, totally unrelated to Prolene which will, for the most part, react very differently than Prolene or PP. Another matter inappropriate for consideration in this matter.

Plaintiff's expert also refers to Costello,[363] who for a large segment of his work did not use Ethicon products. All 14 samples included in the Costello study were the polypropylene components from polypropylene/expanded polytetrafluoroethylene composite hernia mesh such as Composix E/X or Kugel Composix (C.R. Bard, Cranston, RI). Costello states, "After explantation, the meshes were immersed in a 10% v/v formalin solution and stored at room temperature. Prior to testing, any adherent tissue was removed from the meshes by soaking in a sodium hypochlorite solution for 2 h at 37^{o}C (6–14% active chlorine, Sigma Aldrich, St. Louis, MO). Each mesh was then rinsed several times with distilled water to remove any residual sodium hypochlorite solution and allowed to dry overnight."

Given these mild cleaning conditions, it is abundantly clear that the explants were not free of proteins when tested. There was no FTIR data collected to confirm the degree of explant cleanliness. PTFE has much different surface energy than PP and thus the rationale for its "clean" surface.

Furthermore, Costello used instrumental techniques such as SEM, DSC, and TGA but the ability to identify chemical moieties or constituents was absent, as no FTIR analytical work was

performed. The SEM data is unreliable in that explants were fixed in Formalin solution, sputtered with Gold, and no consideration was given the well-known Formalin-Protein fixation chemistry, as well as the drying process from which artifacts are easily produced. It is not surprising, but expected, that micro-cracks would be observed under SEM observation. The DSC data noted a "shift toward a lower melting temperature," although the changes observed were not considered statistically significant. Costello's TGA data was summarized and supports the concept of Prolene stability as, "In contrast, the explanted lightweight polypropylene specimen showed weight loss almost identical to that of its pristine counterpart, suggesting that weight was not lost while *in-vivo*."[364]

To further confuse the matter the following quote is included from Costello, *et al.* "As expected, the majority of the explanted polypropylene specimens showed significantly less weight loss during TGA as compared to the pristine Composix E/X specimen, further strengthening the argument that these materials underwent oxidation *in vivo*."

Plaintiff's expert references Mary, *et al.*[365] as having reported "adherent macrophages and FBGC have been reported to infiltrate PP mesh."[366] However, Table 2 of the Mary article contrasting PVDF and Prolene reports duration of implantation and identity of "Macroscopic and Microscopic Observations at the Surface of Polypropylene Sutures After Implantation…" from 4 hrs. of implantation to 2 years. In describing the data for Prolene (Table 2), Mary notes that "Microscopic observations of the anastomoses after periods between 3 months and 2 years revealed that both sutures (PVDF and Prolene) were encapsulated in thicker collagenous tissue without any invasion by inflammatory cells." These data are contradictory to plaintiff's expert writings.

Most notable among the Mary article is the quote, "Both pure polymers are devoid of this functional group," (PAGE 201-DX30945.3). By way of explanation, the authors used FTIR spectroscopy as a means of gathering data and drawing conclusions. However, they elected to perform FTIR spectroscopy evaluations at only one wavelength, i.e. 1740 cm^{-1} and unknown to the authors Prolene's DLTDP absorbs at this frequency. The intent was to show presence of carbonyl group formation *in vivo* and thereby oxidation and molecular weight loss. However, the authors were unaware Prolene contained carbonyl containing chemicals absorbing at 1740. They erroneously concluded therefore that Prolene degraded *in vivo*. Consequently, the Mary article should be dismissed as a reliable data source.

The DePrest reference (21) of plaintiff's expert report does not involve Ethicon products. The products are manufactured by Tyco Healthcare and are multi-filaments implants. The following is a quote from the expert report, "In a recent study characterizing the foreign body reaction of PP implants in a rat abdominal wall model, macrophages and foreign body giant cells were observed both in the tissue surrounding the implant and also the implant itself." One wonders how plaintiff's expert could possibly draw any conclusions regarding Ethicon's Prolene from this article.

Plaintiffs experts Figure 7, Oxidative degradation of PP mesh *in vivo,* is a continuation of data misrepresentation in that Plaintiffs expert describes stained samples in the following way, i.e. "trichrome stain shows that the deeper parts of the "bark" have smaller staining porosity (red)

than those close to the surface (green) which correlates with TEM findings, etc." It is well established science and chemistry that staining is not porosity dependent but instead must involve chemical bond formation between a stain and a substrate.[367] Residual stains, those that do not chemically react with tissue, are washed away during the staining process.

The SEM photomicrographs (Fig.7) of Guelcher's report are not of Ethicon Prolene but of an explanted Boston Scientific, Pinnacle Mesh as per A. Imel, T Malmgren, M Dadmun, S. Gido, J Mays reference from Biomaterials, 2015 titled "In vivo oxidative degradation of polypropylene pelvic mesh."

Section 3 – The dynamic environment where the Prolene mesh is implanted coupled with the foreign body reaction leads to oxidation, chain scission, reduction in molecular weight embrittlement, degradation, flaking, pitting, and cracking.

Plaintiff's expert turns again to Mary[368] and then to Clavé.[369] In the former instance, Mary used a rigorous sample preparation protocol in that samples were "fixed" in glutaraldehyde, and post-fixed with osmium tetroxide, a chemical reaction involving bond formation. Thus the aldehyde and protein "Fixation process" was affected. It was followed by drying by immersion in ethyl alcohol solutions, followed by critical point (at -70^{o} C) using carbon dioxide. The samples were then coated with sputtered gold palladium and viewed with SEM. I would be surprised if cracks were not observed given the aldehyde-protein fixation product was not fully removed, explant drying was affected under very rigorous conditions, and physically manipulated. The protocol used clearly favors extensive sample preparation artifacts formation. In the latter case, Clavé has shown, with the study of 100 explants, Prolene is stable and does not deteriorate in the human body, although the title of this article would suggest otherwise to the non-serious reader. One who did not examine and read this article closely would likely adopt the erroneously worded title as the "article conclusions." We know from our work and that of the plaintiff's expert that what is proposed concerning Prolene degradation herein does not occur, for instance:

- Plaintiff experts have been unsuccessful providing scientific proof of oxidatively derived carbonyl absorptions for implanted Prolene. The spectra of Ca Stearate and DLTDP absorptions have been confused and mis-assigned as representing oxidative degradation. Consider the work of Dunn[370] via Bridget Rogers. This represents a classical example of reporting meaningless data, strongly suggesting plaintiff experts do not understand the underlying chemistry and composition of the Prolene fiber and the formalin-protein chemistry involved in the explanting process. The Rogers data also represents a failed effort to show Prolene oxidation would occur when chemically oxidized.
- Wood utilized a BARD material, and there has been previous testimony that the polymer did not possess UV stabilizers.
- Clavé is mistaken when he addresses the issue of "The diffusion of organic molecules into the polymer (especially esterified fatty acids or cholesterol) may be a cause of the polymer structure degradation." Burkley's work confirmed toughness increases with implantation time, and these property enhancements are due to *in vivo* plasticization effects. Moreover, the report of Mays, expert for plaintiffs, is in agreement with the

concept of plasticization and performance enhancements, to which I agree and have included in this, and prior reports.

- Mary's FTIR data did not account for the presence of DLTDP, an antioxidant, and part of Prolene's formulation. DLTDP holds a carbonyl moiety which Plaintiff's experts have erroneously attributed to that of carbonyl formation by oxidation of Prolene.
- Clavé used a cleaning method we have shown insufficient to remove (all) proteins from PP fibers. The difficulty in removing formaldehyde-protein composite from explants has been confirmed by Dr. Robert Guidoin as well.[371] Thus any data obtained by Clavé is suspect given his conclusions are based on the premise that Prolene fibers are "clean."
- Clavé's control group samples (pristine samples of Prolene® and Prolene Soft®) were treated with the same protocol to determine if the cleaning process had chemically modified the material. Spectra from test groups were compared to their specific control spectra. Consider the following statements:

    - FTIR absorption bands between 1,615 and 1,650 cm^{-1} could be attributed either to carboxylate carbonyl from Calcium Stearate, fatty acids, or residual products of biological origin. Therefore, these data alone cannot confirm the formation of carboxyl groups *in vivo*.
    - No modification was observed in the melting temperature or heat of fusion of these samples. Thus, if an oxidation occurs in these prosthetics, it takes place in the amorphous zones, and crystallinity is preserved.

- Several hypotheses concerning the degradation of the PP are described below. None of these, particularly direct oxidation, could be confirmed in this study.
- The FTIR analysis neither confirmed nor excluded oxidation of PP in the in vivo environment.
- In this study, no difference between DSC thermograms of pristine and "degraded" samples was found. Additionally, FTIR analysis did not conclusively confirm that the degradation was due to oxidation.
- Additional chemical analysis such as thermogravimetric analysis and molecular weight determination, specifically, would further clarify the mode of prosthetic damage.

It is irrefutable, Clavé has confirmed, by his work, Prolene does not meaningfully degrade in the human body, with perhaps ophthalmological sutures exposed to UV light being an exception on an infrequent basis.

Section 4- PP mesh is known to fray under tension and release particles while handled and implanted. The human body does not stop responding to these particles or to the PP mesh unless the product is removed in its entirety

Plaintiff's expert once again turns to polyetherurethanes examples used as pacemakers in an attempt to associate polyurethanes as a chemical class and known to be susceptible to environmental stress cracking with PP. PP is a dramatically different polymer type, possessing only carbon and hydrogen, and known not to undergo stress cracking. Polyurethanes on the

other hand will exhibit ESC. None of the writings in this section have merit in the matter at hand.[372]

Section 5. Ethicon's pelvic meshes are intended to last for the lifetime of the patient, but the presence of antioxidants does not permanently protect the PP against degradation, and thus it is not possible to guarantee that these meshes will perform their intended function after implantation.

Plaintiffs continue to dwell on the issue of Prolene's stabilization although no evidence exist to seriously question the excellent synergistic performance of Santonox R and DLTDP. This combination of stabilizers has performed extraordinary well for more than five decades. I have repeatedly shown SEM photomicrographs of explants with essentially pristine surfaces, proving the excellence of Prolene and the Ethicon stabilizer system. As plaintiff's expert's report states, "the eventual *in vivo* induction time for stabilized PP has not been reported,"[373] yet Prolene's history would argue its lifetime exceeds 50 years.

Section 6. The effects of oxidation on the stability of Prolene were known to Ethicon prior to launching its SUI and POP devices, but the company did not consider the risks associated with polypropylene oxidation on the stability of Prolene mesh, to the detriment of patients implanted with the devices.

The extensive work of Ethicon's employee's study of Prolene has been exemplary. Documents I have read confirm Ethicon received and responded to comments, questions and concerns in a serious and professional manner.

Ethicon employees have recognized the potential for ophthalmic sutures exposed to ultra violet radiation to be susceptible to rupture. It is known that PP will degrade when exposed to ultraviolet (UV) light over time. Indeed, Ethicon did establish a Prolene Microcrack Committee to study and confirm the tenet of Prolene's stability *in vivo*. Dr. Peter Moy was among a number of Ethicon employees who received and studied reports of Prolene's performance. He offered, as research scientists do, possible mechanistic routes for Prolene reactions. However, he like many others, then and now, did not fully understand or appreciate the importance of protein (collagen) adsorption onto Prolene and the formalin-protein composite formation. Likewise, the difficulty in removing "fixed proteins" from Prolene's surface was not resolved. I have discussed the basic chemistry of formaldehyde and proteins (known for more than 60 years) and the "fixation" process herein. It cannot be dismissed as it plays a major role in one's ability to accurately and correctly examine Prolene explants. This thesis is echoed by Dr. Robert Guidoin, the provider of hundreds of explants to Ethicon[374] and one whose writings are frequently referenced by plaintiff's.

Furthermore, Ethicon responded to the possibility of oxidation, degradation and concerns with *in vivo* stability in general, and implemented a multi-year study which began in 1985 and ended in 1992. The plan was to be 10 years in length initially, but animal deaths were more than expected and the study necessarily terminated after 7 years. However, the study was profoundly helpful in understanding the *in vivo* stability and durability of Prolene sutures. Much

of the dog study has been discussed in more detail earlier in this report than it will be at this time. In summary, the report confirmed the following:

- Physical property data including tensile strength, elongation, modulus and toughness obtained for Prolene sutures over a 7 year period *in vivo* proved Ethicon's stability. These physical properties improved significantly over time with implantation.
- Molecular weight determinations by GPC once again confirmed Prolene's *in vivo* chemical stability (as did the physical properties just noted). No significant molecular weight changes were noted for the 7 year period. Simply put, Prolene's molecular weight essentially did not change *in vivo* during the 7 years of implantation.
- Prolene's structure was not altered, and its physical properties improved with implantation.
- The Dog Study was successful, by once again confirming Prolene's stability, and thus its suitability for use in the human body. These data were consistent with Prolene's 60+ years leading the suture marked.

Plaintiffs expert write of his work with $CoCl_2$ and hydrogen peroxide designed to accelerate chemical reactions that "might" take place in the future. In doing so, Guelcher designed experiments establishing unrealistic *in vivo* oxidation reaction conditions and they did not oxidize Prolene. E. Rene de La Rie offered words of wisdom and caution for scientist who take the plaintiff's expert approach.[375]

The following nine issues are taken from De La Rie on Polymer Stabilizers (a reference offered by Plaintiffs expert):[376]

1. Additives, at low concentrations (typically 0.25 – 3.0%), inhibit degradation processes that cause loss of the original properties of the materials.
2. Hindered phenols (Santonox R) are hindered phenols and as such are radical scavengers since they react with peroxy ($ROO^{\cdot}$) and alkoxy radicals ($RO^{\cdot}$) to form phenoxy radicals, which are relatively stable because of resonance stabilization and steric hindrance.
3. Sulfur compounds (DLTDP): Various sulfur compounds have antioxidant activity. They are mostly used in conjunction with phenolic antioxidants (Santonox R is an example)."
4. Synergism-Mixtures of two or more different types of additive often have a greater effect than the sum of the individual effects. The phenomenon is called synergism.
5. The authors speak further to the issue of accelerated weathering noting that "it would be impossible to over emphasize the importance of choosing the proper accelerated aging technique and the correct material properties under study for evaluation."
6. Care should be taken with the interpretation of the results of accelerated aging.
7. The assumption that reaction mechanisms remain the same as long as radiation of the same spectral output is employed and that the reaction rate increases linearly with the intensity (or concentration of reagents) is not always justified. At the high light levels employed in accelerated aging devices, concentration levels of free radicals may be obtained that never occur during natural aging.
8. If temperatures used are considerably higher than those exposed to under normal circumstances, the danger exists of introducing new degradation reactions.

9. Heat aging tests of materials normally exposed to UV light are not likely to be valuable since photochemical oxidation is generally much more severe than thermal oxidation (below 200^{o}C)

Finally, I was unable to confirm Plaintiff's expert testimony that ROS stronger than hydrogen peroxide was confirmed in any of his 47 references.

Plaintiff's expert report includes various comments regarding the work of Dr. Peter Moy of Ethicon who, some 30 plus years ago, studied the concept of Prolene degradation. Dr. Moy was exploiting every avenue he felt helpful and during his investigation of Explant 83-136 utilizing 400X magnification. He noted that when his specimen being examined was heated, the following occurred: "heating at 150 °C where the fiber softening with an increase in fiber diameter, the cracked layer peeled from the fiber cleanly." "The fiber continued to contract under similar internal stress to the melting point of Prolene (165 °C) at which time the fiber was completely melted, but the cracked layer maintained its form."[377] I provided underlined portion for emphasis. He opined, "The thermal stability of the cracked layer leads to two possibilities; 1) the layer is crosslinked polymer or 2) it is proteinaceous in nature. He was correct on both accounts. He concluded this study with the following statement, "---the evidence presented tends to favor a biological origin for the microcrack layer---. "Indeed, the cracked layer was crosslinked as Dr. Moy suggested, and it was proteinaceous. The crosslinked protein-formaldehyde composite formed around the fiber while the protein containing explant was stored in formaldehyde.

Thus more than 30 years ago an Ethicon employee performed experiments while searching for a reason crack formation might occur, and confirmed substrate cracking was proteinaceous in nature. His work and conclusions at that time are consistent with my work and conclusions today.

The work of Professor Guidoin has been addressed elsewhere and will not be repeated. However, it should be noted Dr. Guidoin published on the topic of cleaning explants and the difficulty of removing biological and proteinaceous matter could require strong chemical treatment.[378]

Section 7. PP mesh is not inert and its properties change after implantation, which can lead to adverse events in an implantee.

Burkley's data confirm improvement in physical properties during and after 7 years of implantation. No significant molecular weight changes occurred during, and after 7 years, implantation and thus while physical property changes did occur for Prolene in the dog study, i.e. they constituted significant property improvements.

Plaintiff's expert reference to the Wood article omits the fact that PP in that study was not Prolene. Moreover, earlier testimony was submitted stating that the PP in question had no added stabilizers.

Plaintiff's expert references including Clavé and Costello's comments are inconsistent with their written documents. For instance, I have responded to Clavé work earlier, i.e. "Clavé has shown, with the study of 100 explants, Prolene is stable and does not deteriorate in the human body, although the title of this article would suggest otherwise to the non-serious reader. One who did not examine and read this article closely would likely adopt the erroneously worded title as the "article conclusions."

Costello[379] used a C.R. Bard, Composix E/X mesh, to which I have already commented, not Prolene. It is also important, however, to once again emphasize after explants are surgically removed, they are placed in 10% formalin and stored at room temperature. There are infrequent exceptions to this protocol. When explanted tissue and formalin comes in contact, a chemical reaction between formalin and body proteins begins and continues over time producing a hard, brittle, composite shell or armor around the explanted fiber. These authors noted prior to testing, attempts to remove adherent tissue from the meshes involved soaking in a sodium hypochlorite solution for 2 hrs. at 37 °C. We have learned from our work such cleaning conditions are insufficient to completely remove the formalin-protein composite polymer. Moreover, no scientific data was produced to show the degree of explant cleanliness. For instance, FTIR spectroscopy data could provide that information, but FTIR was not performed. Our FTIR work has shown mild cleaning conditions, as noted, do not remove all the formaldehyde-protein composite fixation layer. Therefore, the remaining data and conclusions are suspect as the authors were unaware of the remaining adsorbed and adhered surface layer of protein-composite.

Plaintiff's expert continues to refer to polyether-urethanes and their deficiencies with respect to degradation of their polyether component and subsequent loss in molecular weight. However, I once again stress that polyether-urethanes are made of a very different molecular structure than PP. Non-polar PP is composed of carbon and hydrogen only, while the polar urethanes, to which he refers, are composed of oxygen, carbon, hydrogen, and nitrogen; a much different, and highly polar molecule than PP and consequently one susceptible to different chemical reactions than PP. For instance, polyurethanes are broken apart or hydrolyzed by water, and thus can be hydrolytically unstable. To the contrary, PP has essentially no sensitivity to water and is not polar in its chemical structure and composition.

Plaintiff expert report states, "If treatment with 30% hydrogen peroxide caused oxidation of the PP suture (as reported by Dr. Moy), then ROS secreted by adherent macrophages would also be expected to cause oxidation." Nothing could be farther from the truth; for instance, I see no evidence that plaintiff's expert has knowledge of a specific concentration of ROS *in vivo*, and/or its relationship to Prolene's immersion in 30% hydrogen peroxide for one year. Furthermore, Dr. Moy has shown immersion in 30% hydrogen peroxide for one year will not and did not oxidize Prolene.

Patient Explant Analysis

I have testified in other mesh cases and hereby incorporate my prior reports and testimony.

In support of my opinions, I have examined multiple Prolene product explants from multiple patients and include excerpts from prior testing to visually and spectroscopically demonstrate the reasons for my scientific opinions, and I rely on the results of these analyses.

Analytical techniques used included Light Microscopy (LM), Fourier Transform Infrared Spectroscopy infrared microscopy (FTIR-Micro), and Scanning Electron Microscopy (SEM). At times other chemical analyses and techniques were used and in those cases are included herein.

The chemical reaction detailed in Figure 36, and included here for convenience, demonstrates the reversibility of the protein-formaldehyde crosslinking reaction.

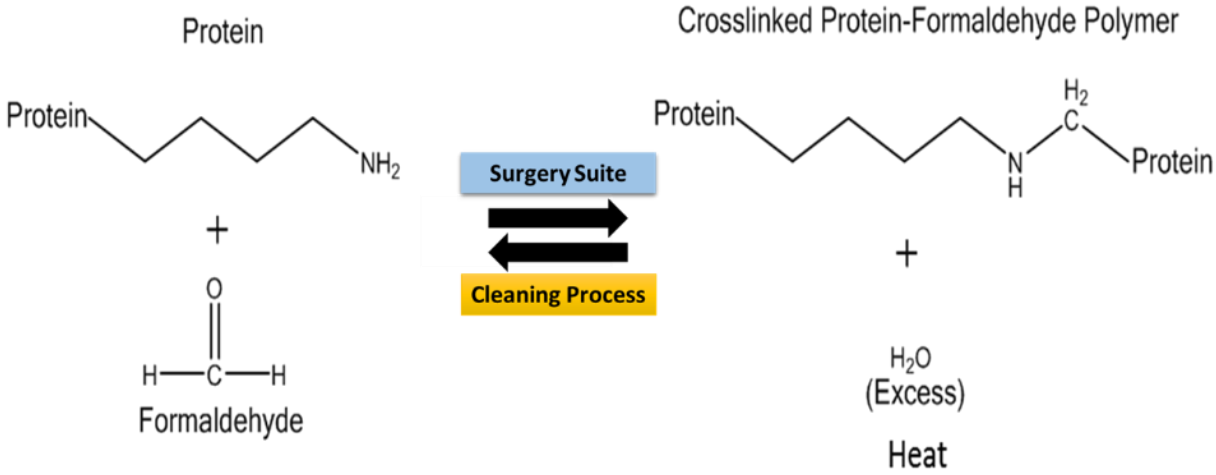


Figure 36. Reaction of protein and formaldehyde resulting in a crosslinked protein-formaldehyde polymer.

This reversible reaction effectively facilitates explant cleaning. This process is necessary to thoroughly clean the explants before analyses, in order to be certain the data obtained represent Prolene and not adhered contaminants. Consequently, I developed a cleaning protocol using distilled water, NaOCl and Proteinase K, based on the reversible formaldehyde-protein reaction (See Figure 36), to clean explants.

Pristine Gynecare Prolift Exemplar – Lot 3026838-120082 and Gynecare TVT – Exemplar – 810041B – Lot 3694576 devices, used as controls in my analyses, are shown in Figures 37 and 38 below.

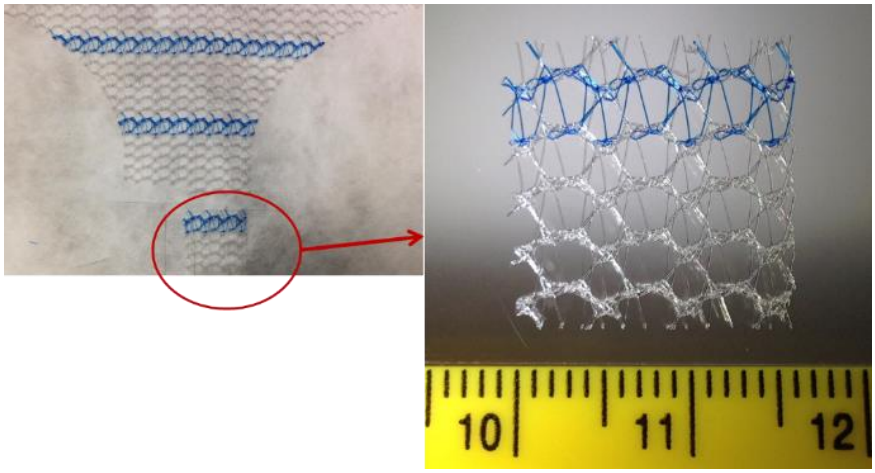


Figure 37. Pristine Gynecare Prolift Exemplar – Lot 3026838-120082

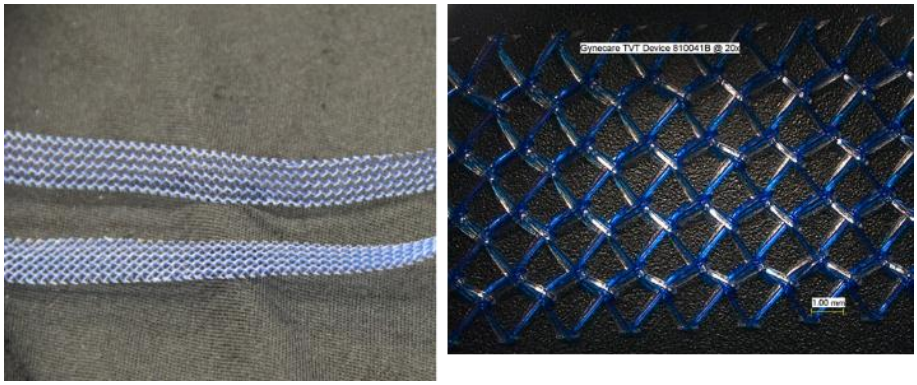


Figure 38. Pristine Gynecare TVT Exemplar – 810041B – Lot 3694576

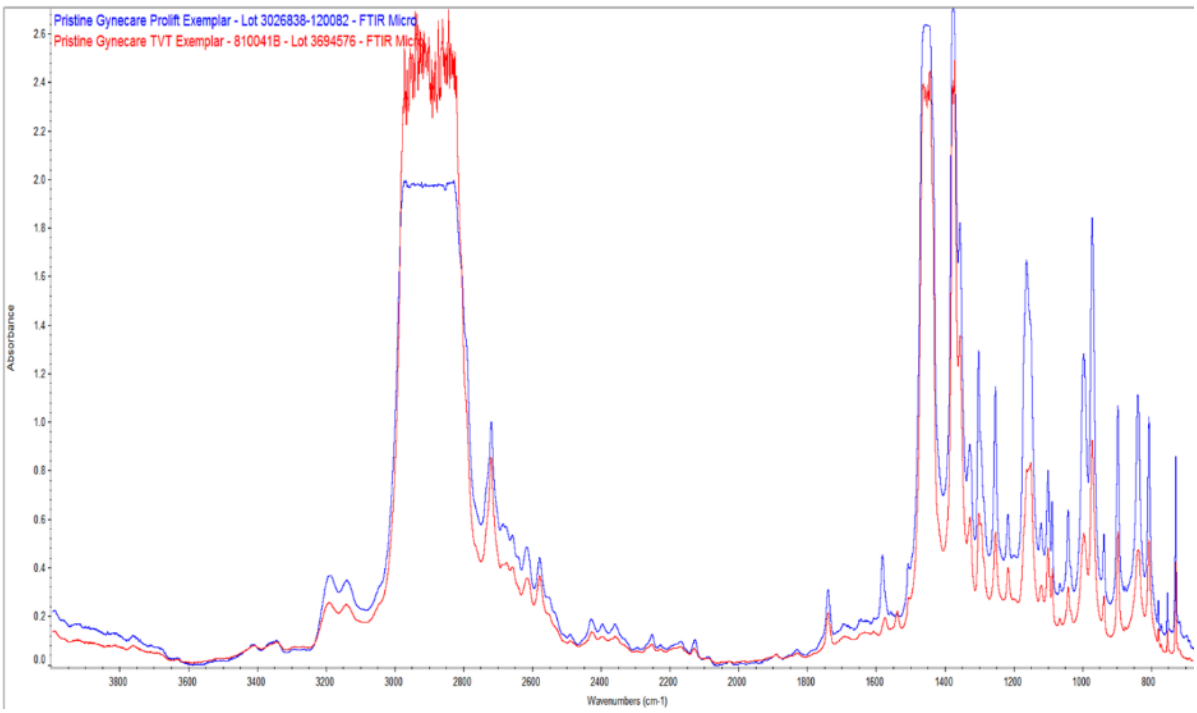


Figure 39. Pristine Gynecare Prolift Exemplar – Lot 3026838-120082 – and Pristine Gynecare TVT Exemplar – 810041B – Lot 3694576 – FTIR Microscopy

Some plaintiffs' experts have opined that spectral absorption at ~1740 cm^{-1} is solely indicative of oxidative degradation of Prolene. However, this FTIR spectral absorption is present in pristine exemplars, Figure 39, and represents the carbonyl group of DLTDP antioxidant, a component of Ethicon's Prolene formulation. A reference spectrum of DLTDP is overlaid with a TVT exemplar spectrum in Figure 40.

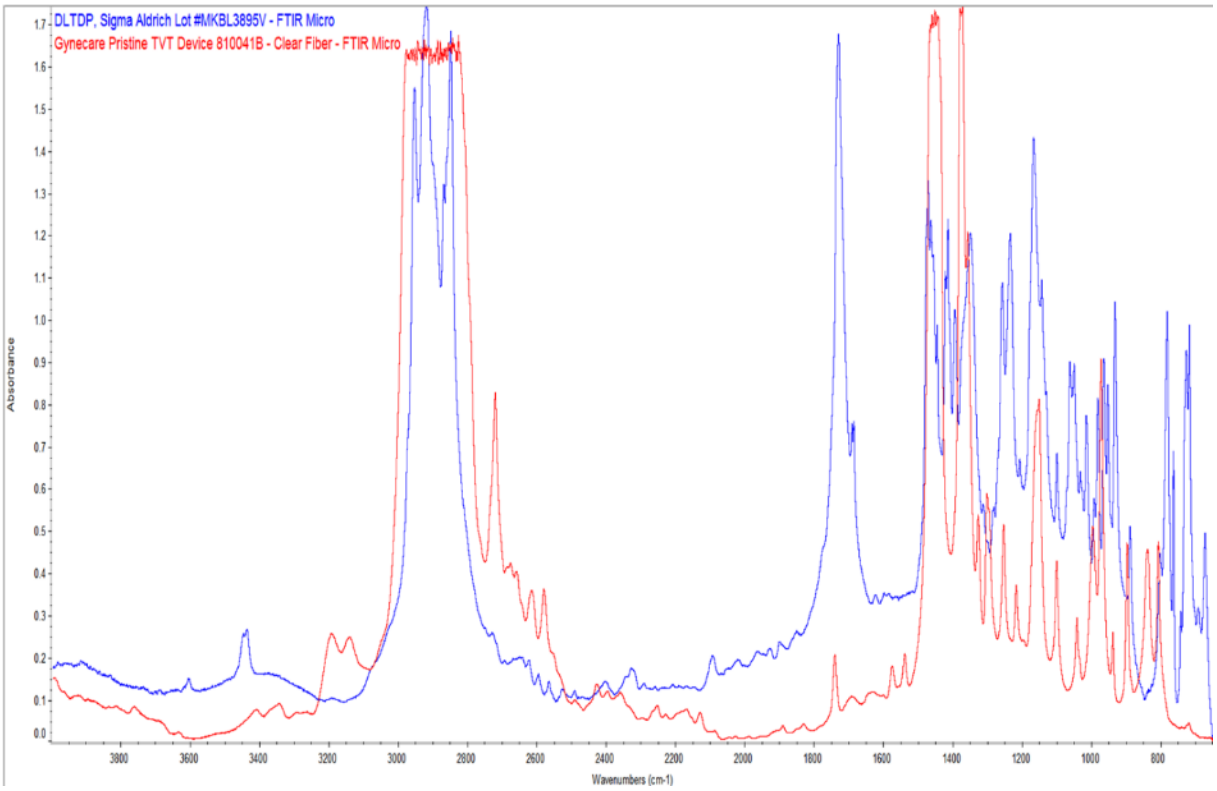


Figure 40. DLTDP overlaid with Pristine Gynecare TVT Exemplar – 810041B – Lot 3694576 – FTIR Microscopy

An excellent example, and utility of SEM imaging, is provided in Figure 41 where the SEM image at 2,910X magnification established a thickness of 3.15 microns for the peeling surface layer of the adsorbed and fixed protein coating layer.

It is helpful in gaining a perspective of 3.15 microns by comparing it to the thickness of a human hair, i.e. (Figure 42) at 69 microns.

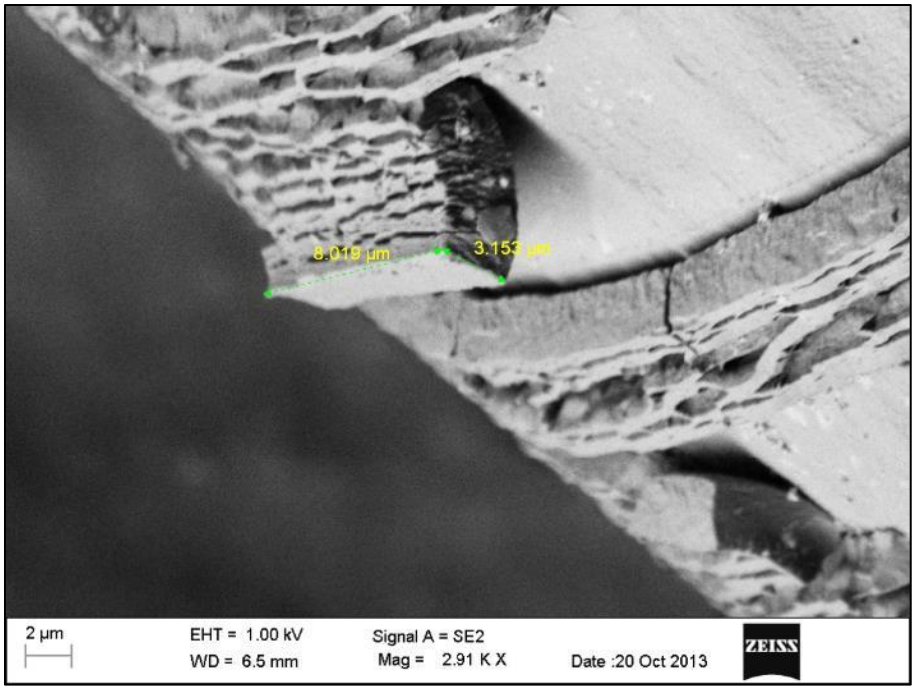


Figure 41. SEM Image of Patient 1 – Exponent Labs Processed Fiber

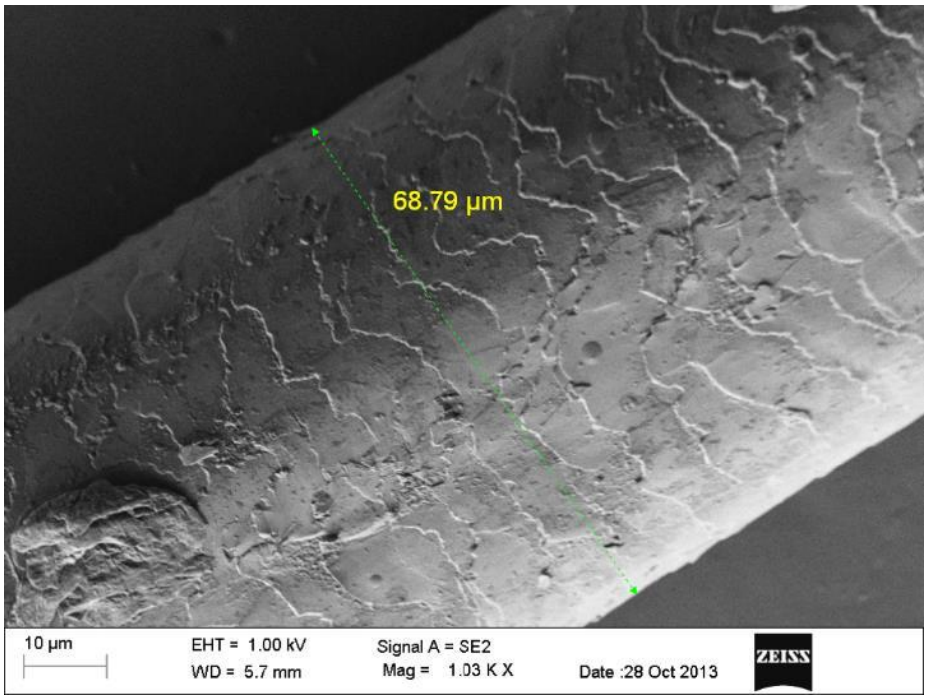


Figure 42. SEM Image of Human Hair

Therefore, the thickness of a human hair is approximately 22 times greater than the protein coating layer identified in Figure 41. Note also that the 3.15 micron protein layer is not an integral part of the smooth Prolene fiber whose extrusion lines continue to be present, are unmodified by implantation, and run perpendicular to the exterior surface layer. The lack of

integration of the two layers is obvious as shown by the dark shadow line representing a separation between layers, one smooth (Prolene) and the other rough (formaldehyde crosslinked protein coating layer). Certainly this would not be unexpected given their chemical difference in composition and difficulty in removing the exterior layer. As the explant was maintained in formaldehyde subsequent to explanting, there was ample time and opportunity for formaldehyde to "fix" human proteins, thereby forming a rigid protein-formaldehyde polymer sheath around the fiber(s) as shown, and adhering to the Prolene surface.[380]

As an example for this litigation, and at my direction, Dr. Kevin Ong of Exponent Labs received tissue and mesh samples explanted from patients. The first example is labeled as Patient 4 #1.1 and Patient 4 #2.1. These explants were preserved in 10% neutral buffered formalin when received. Dr. Ong divided the samples, rinsed and soaked them in distilled water, dried them once again and sent them to me via overnight delivery before any tissue removal or cleaning steps were undertaken. I received the 'before cleaning' samples labeled Patient 4 #1.1 and 4 #2.1, along with an exemplar TVT mesh (810041B, # Lot 3694576) an Ethicon product made of Prolene, the same material at issue in this litigation.

Upon receipt, Patient 4 #1.1 and 4 #2.1 samples were examined via Light Microscopy (LM), Fourier Transform Infrared Spectroscopy (FTIR), and Scanning Electron Microscopy (SEM). The initial data acquired were designated as "Before Cleaning" and recorded. The explants were returned to Dr. Ong with my request to clean the explants according to the cleaning process I developed (see Figure 43. Patient 4 – Exponent Labs Cleaning Protocol). After cleaning according to Step #1 was affected, the "Before Cleaning explants were returned to me for further analyses. This process was repeated for the 5 "After Cleaning Cycle" steps process already noted. Explant examinations were conducted at the following intervals:

- Before Cleaning
- After Cleaning Cycle 1
- After Cleaning Cycle 2
- After Cleaning Cycle 3
- After Cleaning Cycle 4
- After Cleaning Cycle 5

Sample Name	1st Step	2nd Step	3rd Step	4th Step	5th Step	6th Step	7th Step	8th Step	9th Step
Patient 4 #1.1 Patient 4 #2.1 Exemplar	Distilled water. Spray rinse; soak 1 h; spray rinse	Desiccation drying,1 h. Followed by SEM	Distilled water. Water bath (70 ˚C), 42 h; spray rinse	6-14% NaOCl. Shaker, 15 min	Distilled water. Spray rinse; soak 1 h; spray rinse	Desiccation drying, 1 h. Followed by SEM	Distilled water. Water bath (70 ˚C), 40 h	6-14% NaOCl. Shaker, 1 h	6-14% NaOCl. Ultrasonic bath, 1 h
		Before Cleaning				After Cleaning Cycle 1			

Sample Name	10th Step	11th Step	12th Step	13th Step	14th Step	15th Step	16th Step	17th Step	18th Step
Patient 4 #1.1 Patient 4 #2.1 Exemplar	Distilled water. Spray rinse, ultrasonic bath 1h, spray rinse.	Desiccation drying,1 h. Followed by SEM	6-14% NaOCl. Shaker, 4 h	6-14% NaOCl. Ultrasonic bath, 2 h	Distilled water. Spray rinse, ultrasonic bath 1h, spray rinse.	Desiccation drying,1 h. Followed by SEM	Distilled water. Water bath (70 ˚C), 30 h	0.8 mg/ml Proteinase K. Water bath (58 ˚C), 15 h	0.8 mg/ml Proteinase K. Ultrasonic bath, 2 h
		After Cleaning Cycle 2				After Cleaning Cycle 3			

Sample Name	19th Step	20th Step	21st Step	22nd Step	23rd Step	24th Step	25th Step
Patient 4 #1.1 Patient 4 #2.1 Exemplar	Distilled water. Spray rinse, ultrasonic bath 1h, spray rinse.	Desiccation drying, 1 h. Followed by SEM	Distilled water. Water bath (70 ˚C), 48 h	6-14% NaOCl. Shaker, 17 h	6-14% NaOCl. Ultrasonic bath, 2 h.	Distilled water. Spray rinse, ultrasonic bath 1h, spray rinse.	Desiccation drying,1 h. Followed by SEM
		After Cleaning Cycle 4					After Cleaning Cycle 5

Figure 43. Patient 4 – Cleaning Protocol

Beginning with Wave 2, the above cleaning protocol was modified from 25 to 23 steps by increasing the water temperature to 80°C and elimination of the 42 hour and 48 hour water soaking steps. These changes shortened the protocol by approximately 4 days as noted in Figure 44 below.

Sample Name	1st Step	2nd Step	3rd Step	4th Step	5th Step	6th step			
	Distilled Water Soak 1h	Desiccation drying, 1h. Analysis Before Cleaning	Distilled water. Water bath (80 ºC), 20h	NaOCl. Shaker, 3min	Distilled Water. Rinse; Soak 1h; Rinse	Desiccation drying, 1h. Analysis After Cleaning Cycle 1			
Sample Name	**7th Step**	**8th Step**	**9th Step**	**10th Step**	**11th Step**	**12th Step**	**13th Step**	**14th Step**	
	Distilled water. Water Bath (80 ºC), 20h	NaOCl. Ultrasonic bath, 1.5h	Distilled water rinse, ultrasonic bath 1h, rinse.	Desiccation drying, 1h. Analysis After Cleaning Cycle 2	Distilled water. Water Bath (80 ºC), 20h	NaOCl. Ultrasonic bath, 4h	Distilled water rinse, ultrasonic bath 1h, rinse.	Desiccation drying, 1h. Analysis After Cleaning Cycle 3	
Sample Name	**15th Step**	**16th Step**	**17th Step**	**18th Step**	**19th Step**	**20th Step**	**21st Step**	**22nd Step**	**23rd Step**
	Distilled water. Water Bath (80 ºC), 20h	0.8 mg/ml Proteinase K. Water bath (58 ºC), 20h	0.8 mg/ml Proteinase K. Ultrasonic bath, 2h	Distilled water rinse, ultrasonic bath 1h, rinse.	Desiccation drying, 1h. Analysis After Cleaning Cycle 4	Distilled water. Water Bath (80 ºC), 20h	NaOCl. Ultrasonic bath, 4h	Distilled water rinse, ultrasonic bath 1h, rinse.	Desiccation drying, 1h. Analysis After Cleaning Cycle 5

Figure 44. 23-Step Cleaning Protocol

Plaintiffs have been critical of this cleaning process arguing that it would remove oxidized Prolene or as plaintiffs write "…would destroy evidence of oxidation"[381] if present. However, the chemical literature describes PP as a hydrophobic material[382] meaning it "hates" water and as such will not dissolve in water, and resists water vapor and any form of water. Should an oxidized product of Prolene be formed it would not be soluble in water and would remain with the explant. Thus, any oxidized product would be identified by the FTIR spectrum which is performed after each cleaning step. Again, should an oxidized product of Prolene be formed it would present, or be identified by the presence of a carbonyl group (C=O) appearing in the FTIR.[383] I have not observed carbonyl formation in any of the explants I have examined. Observe, for instance, the following FTIR showing a carbonyl group (Figure 45).

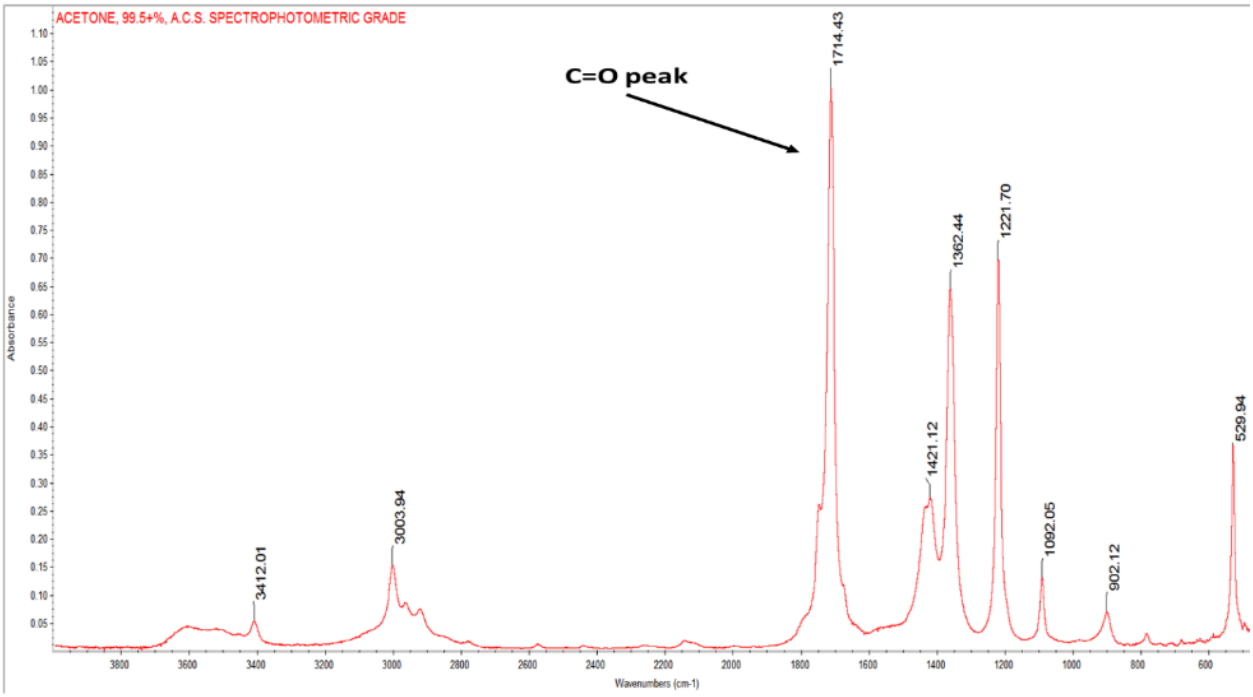


Figure 45. Reference Spectrum of Acetone[384]

Given the Stuart reference,[385] carbonyl groups are a significant absorption frequency and easily identified. No such carbonyl group has appeared in any explant I have examined.

Furthermore, Plaintiff's do not seem to understand that all explants I have examined possess flesh whose composition is high in protein content, and this protein must be removed before a proper examination of the Prolene fiber can be conducted. The cleaning process I developed, and used to clean explants is performed in water, and proteins that possess carbonyl groups, are water soluble. Thus, when the cleaning process of Figure 44 is used, the "reverse" reaction liberates proteins and they are immediately solubilized and removed in the water, as the water is separated from the remaining explant.

Plaintiffs appear confused in that they apparently do not realize that water soluble proteins possess carbonyl groups, as do water INSOLUBLE, oxidized Prolene should such an oxidation reaction occur. Thus, the cleaning process removes water soluble proteins only. If oxidized Prolene was present, it would not be removed by virtue of its water insolubility of any carbonyl over six carbon atoms in length, and it would be identified by FTIR analysis after each cleaning step.

Plaintiffs have also criticized what they call "a lack of a control." However, an experimental control is necessary to control variables. The solubility characteristics of the materials at issue are basic chemistry and not a variable concept. Controls are unnecessary to prove basic chemistry concepts. Proteins possess carbonyl bands and Proteins are water soluble, and that is why they can be removed by the cleaning process. On the other hand, Prolene is not water soluble, and if the explants had oxidized, oxidation carbonyl bands would have formed and the oxidized layer would be insoluble in water and not lost during the cleaning process. However, if an oxidation carbonyl band was present, FTIR would have shown it after each of 5 cleaning

steps. In these cases, the only carbonyl bands shown are protein carbonyl bands, not oxidation carbonyl bands of Prolene.

Before Cleaning

The “before cleaning” samples were examined via light microscopy (LM), scanning electron microscopy (SEM), and Fourier transform infrared microscopy (FTIR-Micro). Figure 46 illustrates the appearance of a pristine TVT mesh (810041B, Lot #3694576) sample. Light microscopy analyses (Figures 47 and 48) depicts the extent to which the explanted mesh was tissue encapsulated.

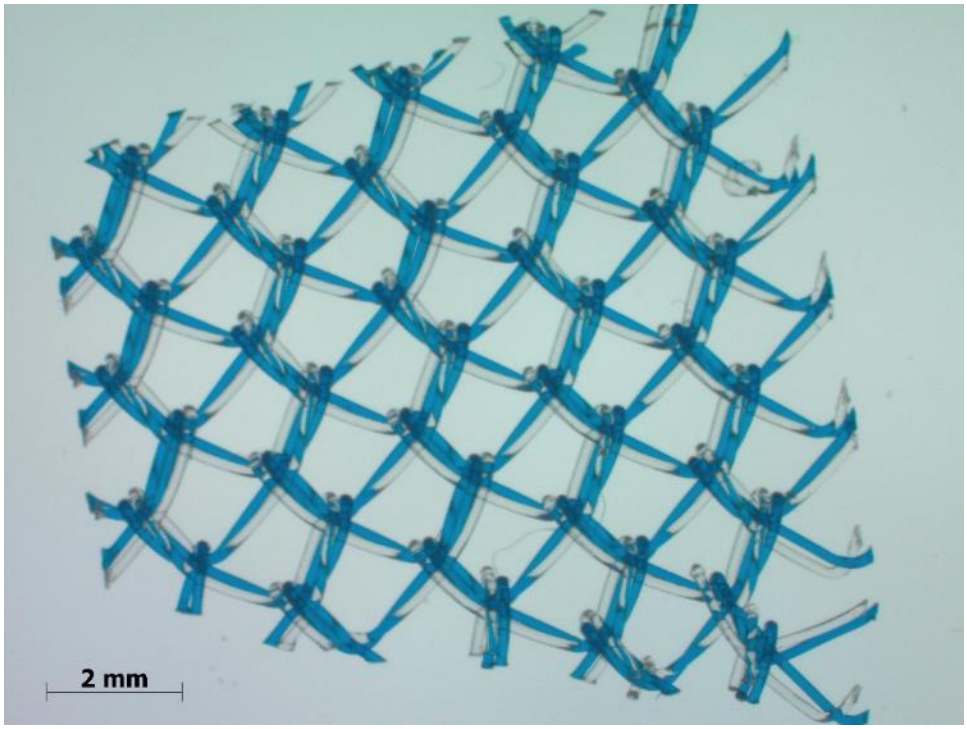


Figure 46. Pristine TVT mesh (810041B, Lot #3694576) – Before Cleaning

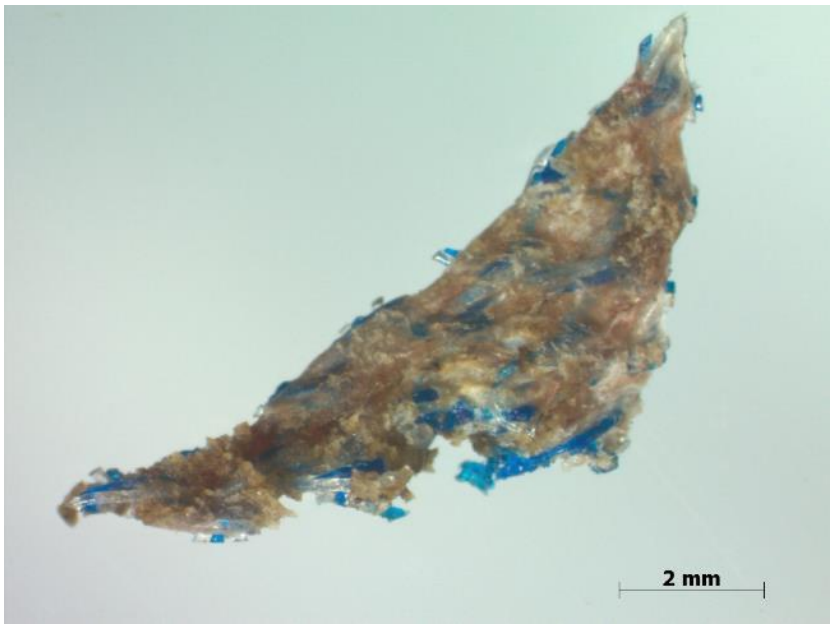


Figure 47. Patient 4 #1.1 sample – Before Cleaning

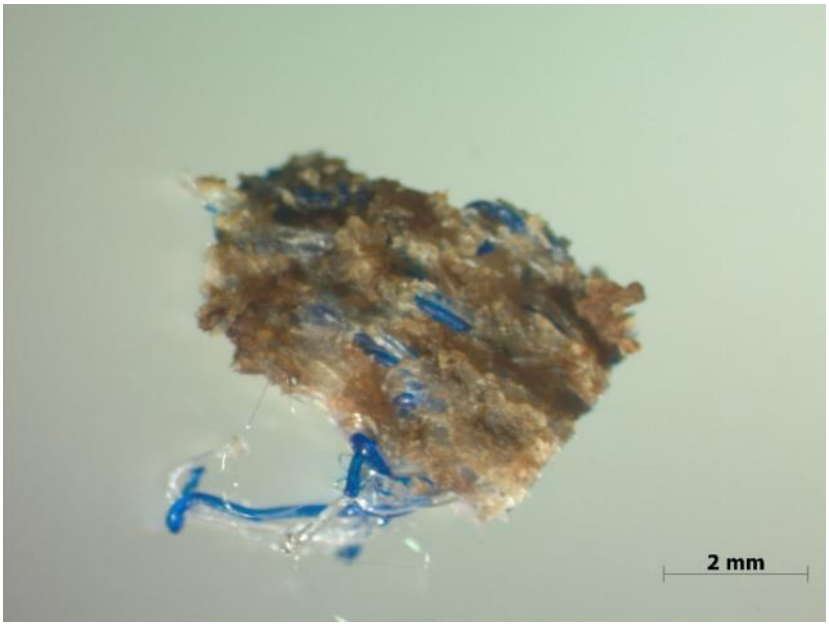


Figure 48. Patient 4 #2.1 sample – Before Cleaning

The explant cleaning progression is illustrated in Figures 49 and 50 and demonstrates the successive cleaning steps of the protocol.

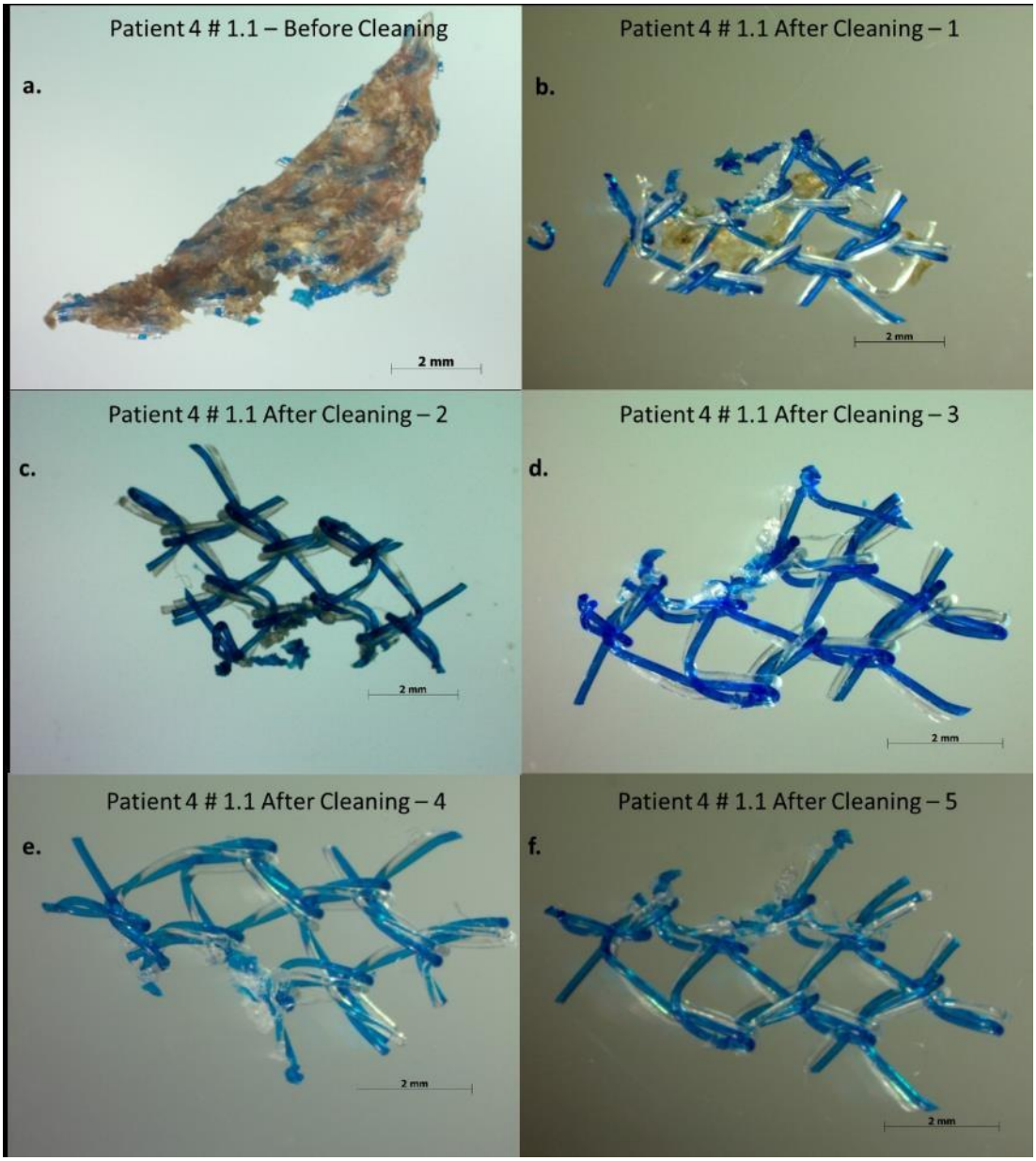


Figure 49. a., b., c., d., e., and f. – Patient 4 #1.1 Light Microscopy

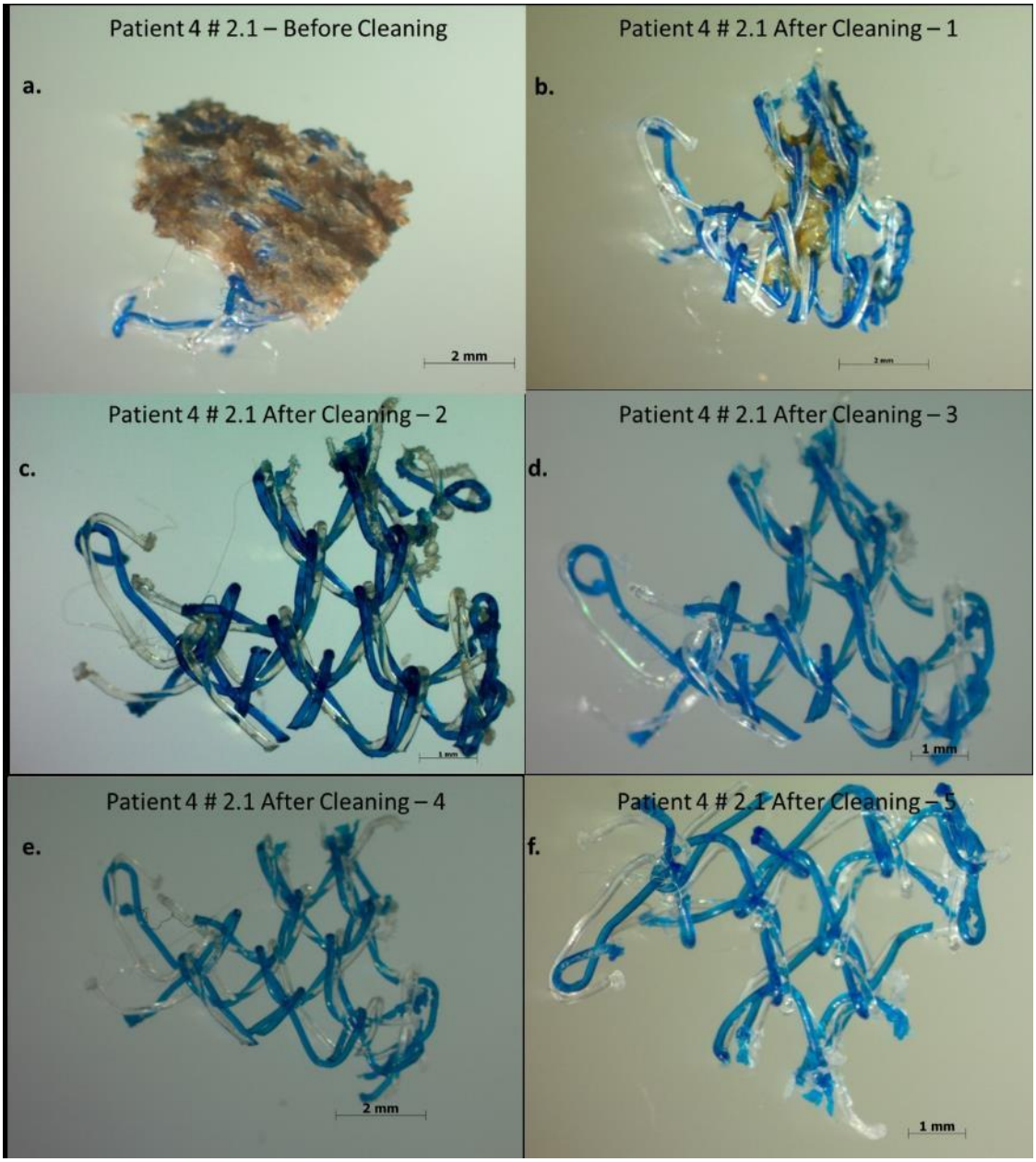


Figure 50. a., b., c., d., e., and f. – Patient 4 #2.1 Light Microscopy

High magnification (200X) shows the Prolene fiber as it is encased within a dry and cracked, proteinaceous layer as noted in Figures 51 – 54, and whose structure was confirmed by FTIR microscopy.

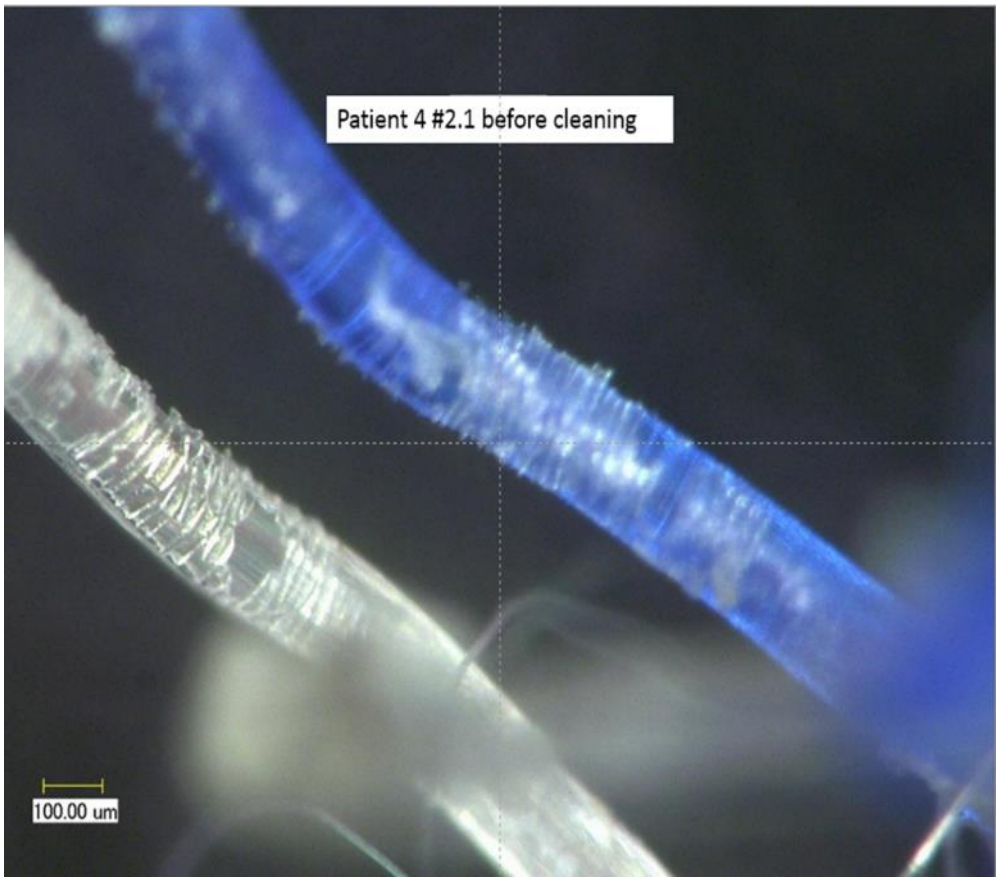


Figure 51. Patient 4 #2.1 – Before Cleaning @ 200X (Fibers outside the encapsulating tissue)

Such data alone are sufficient to defeat plaintiff's consistent and incorrect tenet of *in-vivo* Prolene degradation (See figures 51 – 54) Plaintiffs contend, without any scientific evidence, that Prolene degrades *in vivo* with concomitant cracking, loss of physical integrity and toughness, loss of molecular weight, embrittlement, and so forth. Plaintiffs allege Prolene undergoes surface cracking which leads to these property losses. However, if one simply examines Figures 51 – 54, it is obvious surface cracking and peeling occurs on both the clear (unpigmented) and blue (pigmented) Prolene fibers. Plaintiffs contend the surface cracking material is degraded Prolene. However, this cannot be true. For instance, if the surface cracking and peeling material is degraded Prolene, the unpigmented and supposedly degraded Prolene fibers would be clear. Likewise, the blue and pigmented degraded Prolene fibers would be blue. However, the LM data shows unequivocally that the composition of the material peeling on both the clear Prolene fiber and blue pigmented Prolene fiber is translucent under light microscopy (see Figure 53 and 54 specifically).

This finding does not support plaintiff's theory that the cracked material is degraded Prolene. The LM data are proof positive that the cracked and peeling product is not Prolene.

Moreover, to confirm the “fixation chemistry” and its influence on the structure of explants, additional patient examples of the cleaning protocol described for patient explants are included herein.

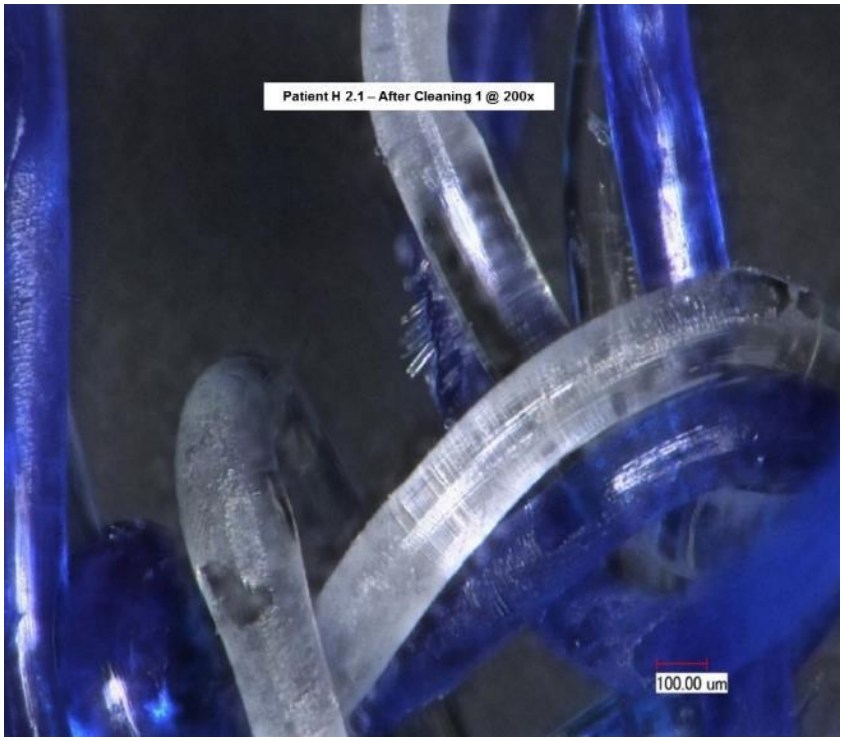


Figure 52. Patient H 2.1 – After Cleaning 1 @ 200X

Figure 53. Patient H2 1.1.1 – After Cleaning Cycle 1 @ 200X

Figure 54. Patient J 1.1 – After Cleaning Cycle 1 @ 200X

To add further confirmation to that of LM, we turned to chemical structure analysis by FTIR spectroscopy.

Chemical Structure Analysis by FTIR Spectroscopy

It is also important to note the identical translucent/clear nature of the cracked and peeled material of both the blue and clear fibers.

> The peeling layer on the blue fiber is clear, not blue, again confirming its composition is not Prolene (Patient 4 #2.1). If it were degraded Prolene it would be blue.

FTIR analyses of the flaked and peeling material from both clear and blue fibers are essentially identical and are further confirmation of the SEM data that the cracked and peeling material is protein, not Prolene. The presence of the thin, translucent protein layer remaining on the Prolene fiber after flesh has been mechanically removed, proves strong protein adsorption and strong adhesive bond formation between the adsorbed proteins and Prolene. The cleaning protocol to which these samples were subjected (Figure 39) confirms, by scientific evidence and experimentation, the extreme difficulty in removing all adsorbed proteins from Prolene. It also proves, unconditionally, that proteins are the flaking material on the surface of Prolene fibers.

The "Before Cleaning" FTIR spectrum (Figure 56) shows spectral components of both polypropylene and proteins as noted by the highlighted 3341, 1650, and 1541 cm^{-1} frequencies. The absorption frequencies are attributed to the protein amide N-H stretching in the 3300 cm^{-1} region, the amide I carbonyl stretching in the region of 1600-1690 cm^{-1} and the amide II stretching and bending in the region of 1489-1575 cm^{-1} as noted by Kong *et al*., respectively and illustrated in Figure 55.[386]

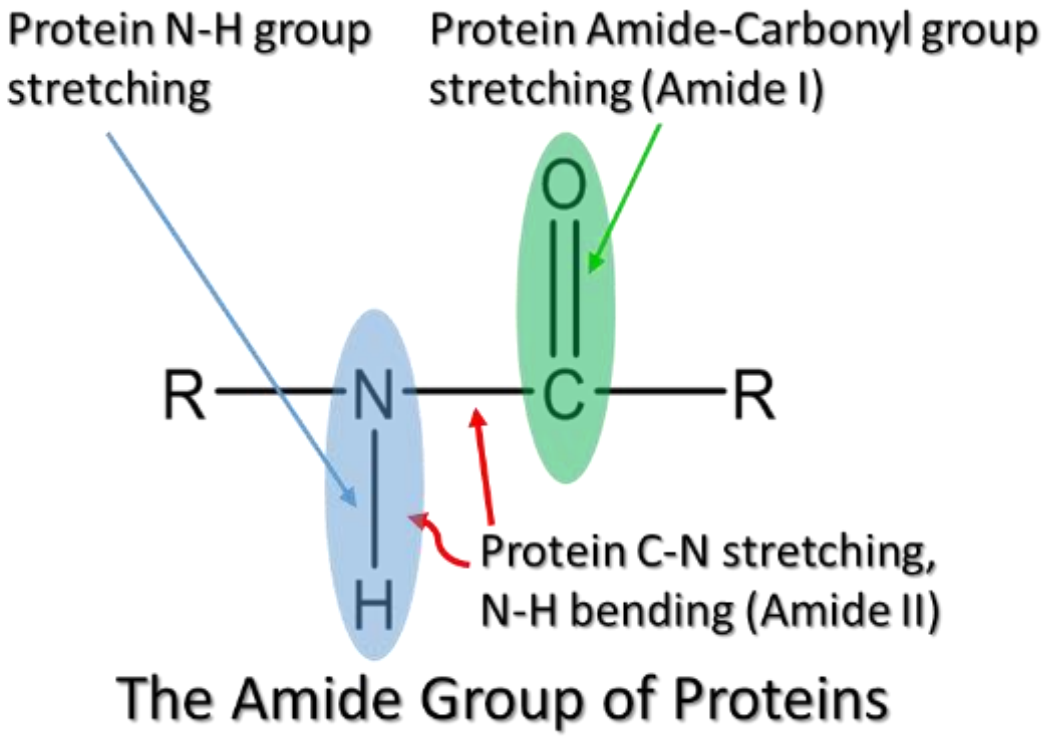


Figure 55. The functional groups of amides

Polypropylene absorption frequencies are also present at 1468 and 1382 cm^{-1}. An overlay of the Before Cleaning fiber and Collagenase (a protein control) are included in Figure 57 demonstrating the overlap in the N-H and amide I peaks of proteins.

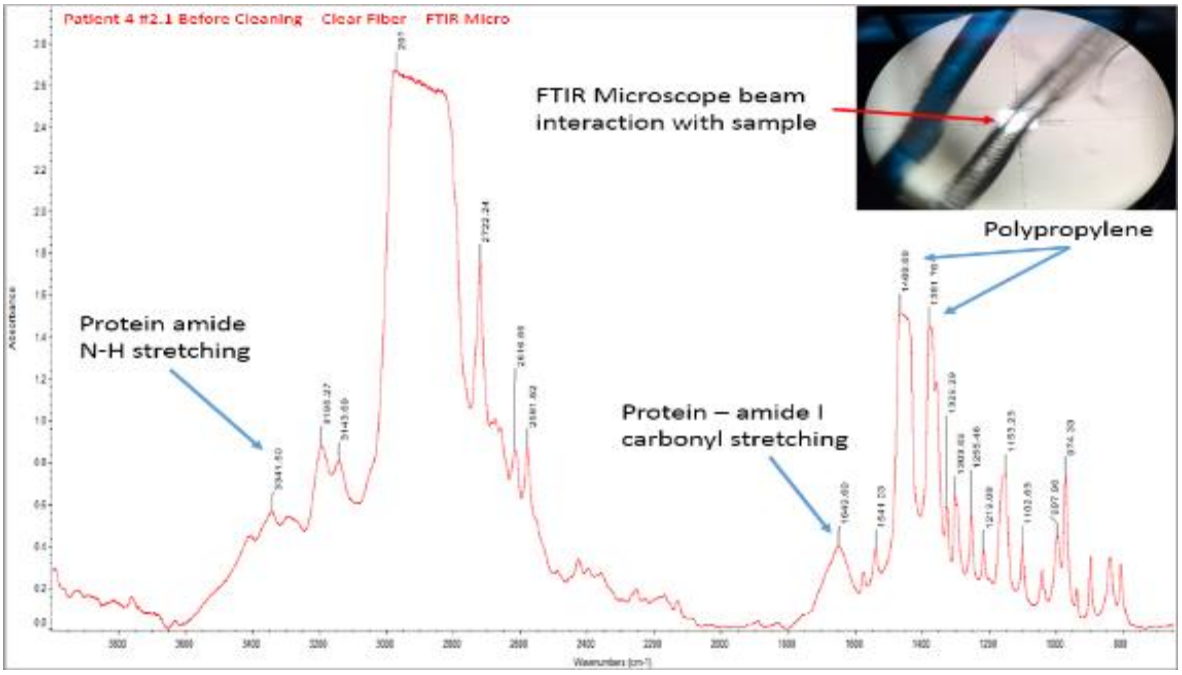


Figure 56. Patient 4 #2.1 – Clear fiber FTIR before cleaning

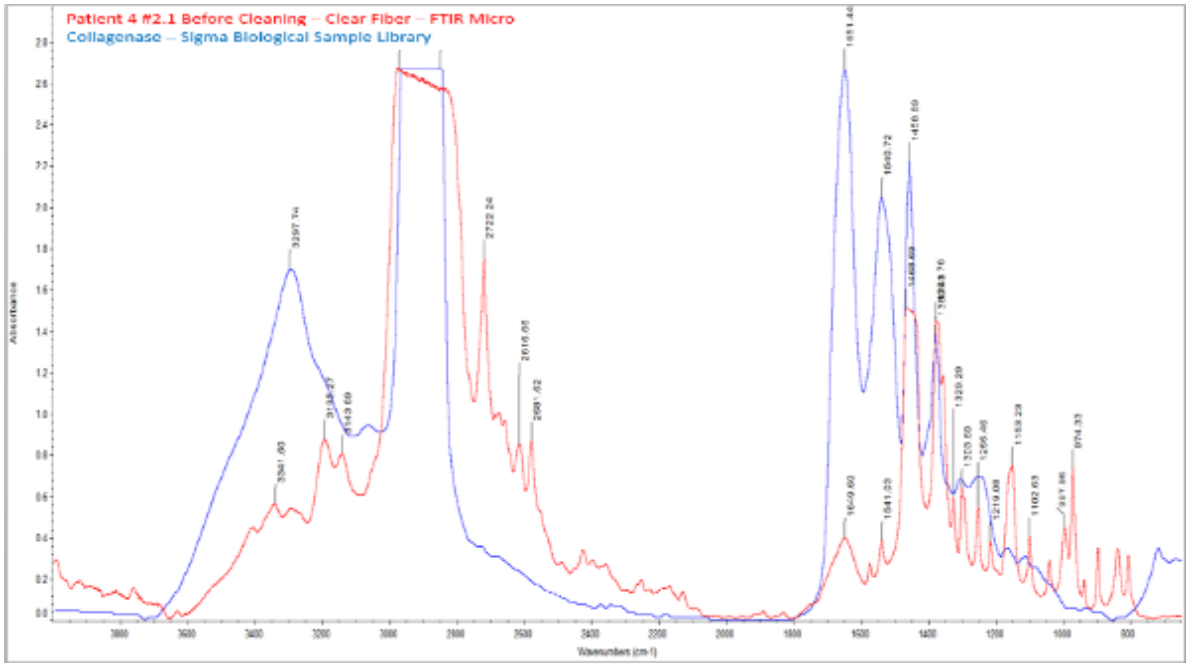


Figure 57. Patient 4 #2.1 – Clear fiber FTIR before cleaning overlaid with Collagenase

The exemplar and two explant samples (#4.1.1 and #4.2.1) were examined before and after the cleaning steps described. These laboratory data establish proteins are adsorbed onto the surface of explanted Prolene before cleaning begins, and a progression of protein removal from Prolene after each cleaning step. This was confirmed both microscopically (Figures 50 and 51) and chemically via FTIR microscopy (Figures 58 – 60).

FTIR analysis proves not only the presence of proteins, but continual removal of adsorbed and fixed protein as each step of the cleaning process is completed. (See Figures 54 – 56). The spectra of Figure 56 have been enlarged to better observe loss of protein absorption intensity with completion of each cleaning step.

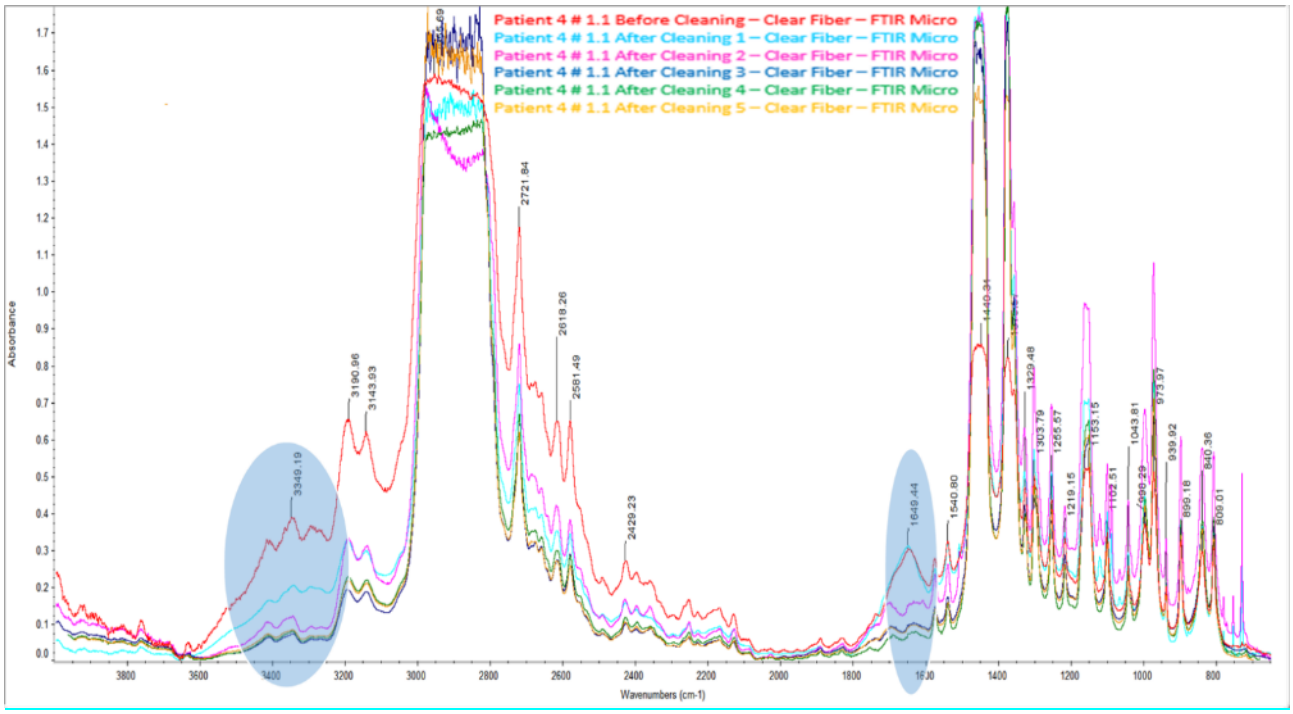


Figure 58. Patient 4 #1.1 – Progressive loss of the adsorbed protein coating with cleaning as confirmed by FTIR Spectra

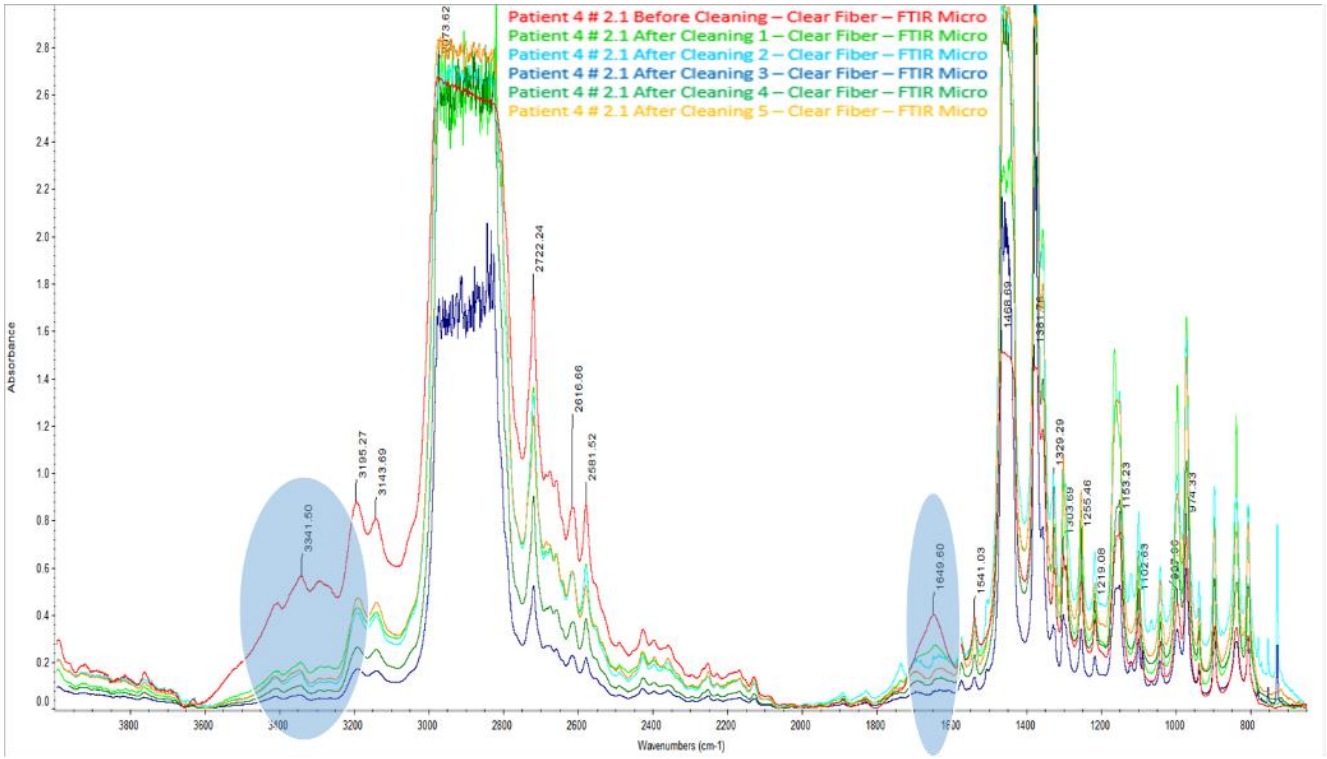


Figure 59. Patient 4 #2.1 – Progressive loss of the adsorbed protein coating with cleaning as confirmed by FTIR Spectra

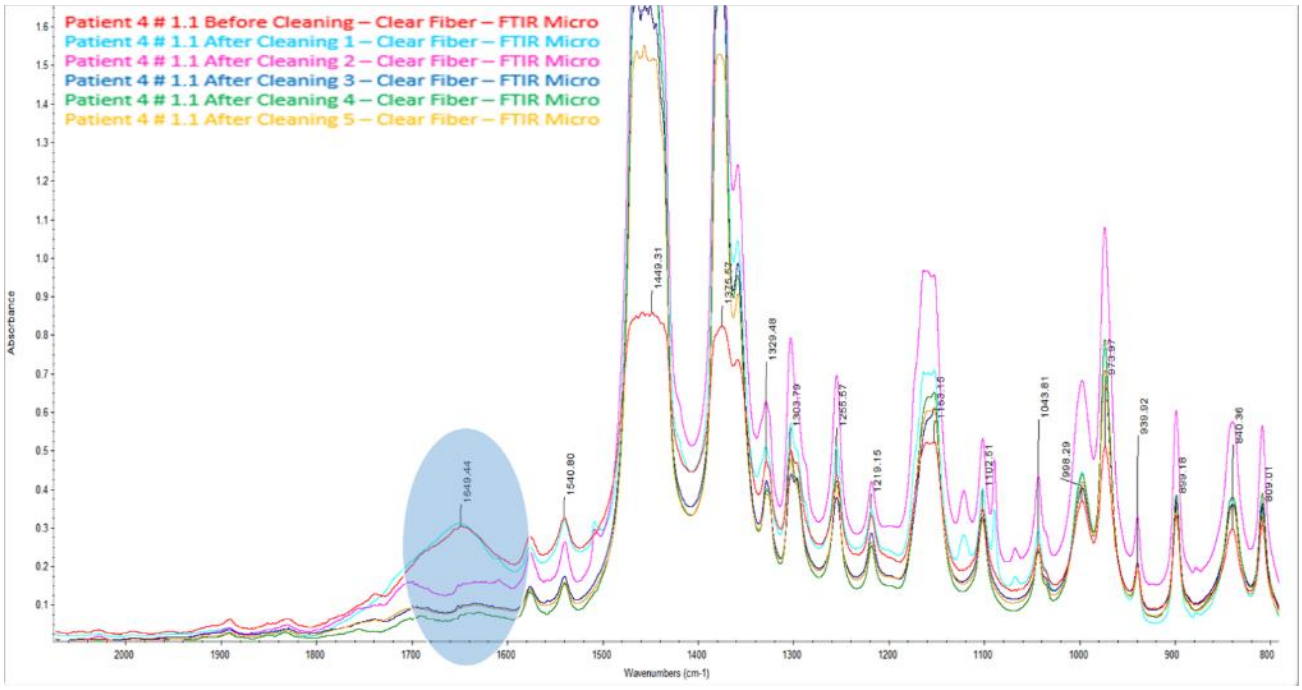


Figure 60. Patient 4 #1.1 – Progressive loss of Amide carbonyl stretching frequency with cleaning as confirmed via FTIR Microscopy – Fingerprint Region

Additional examples of the progressive removal of proteins from other patient explants are included in Figures 61 – 64 below.

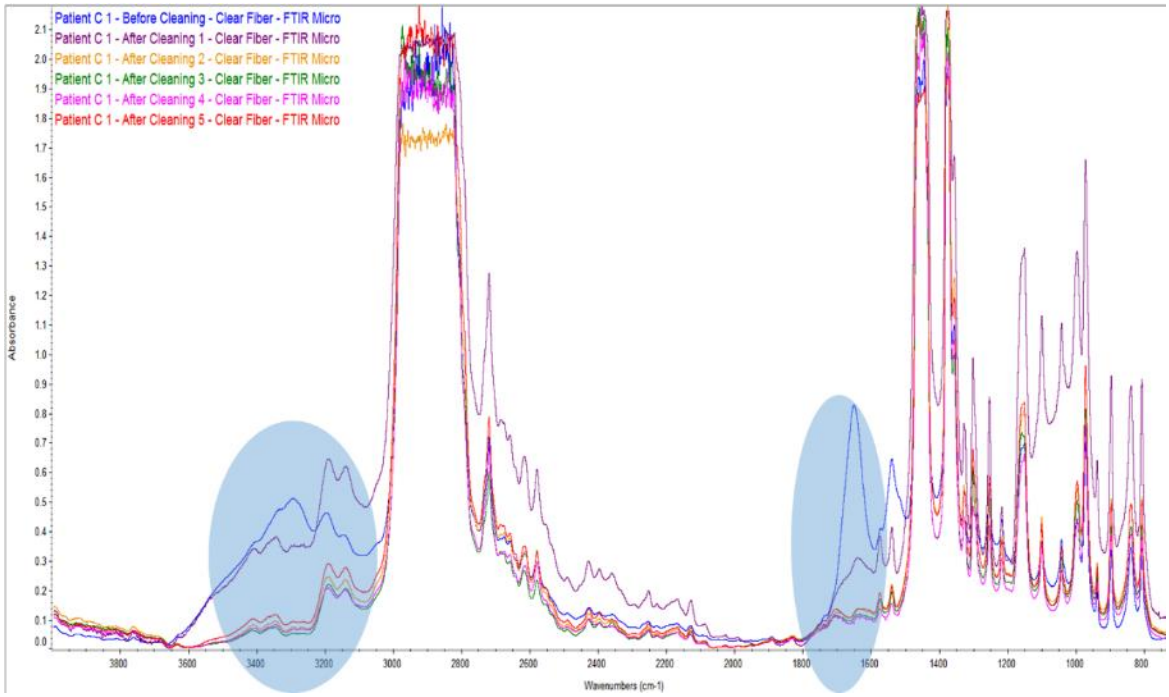


Figure 61. Patient C 1 Example FTIR demonstrating progressive protein removal from Blue Fiber after 5-cleaning cycles

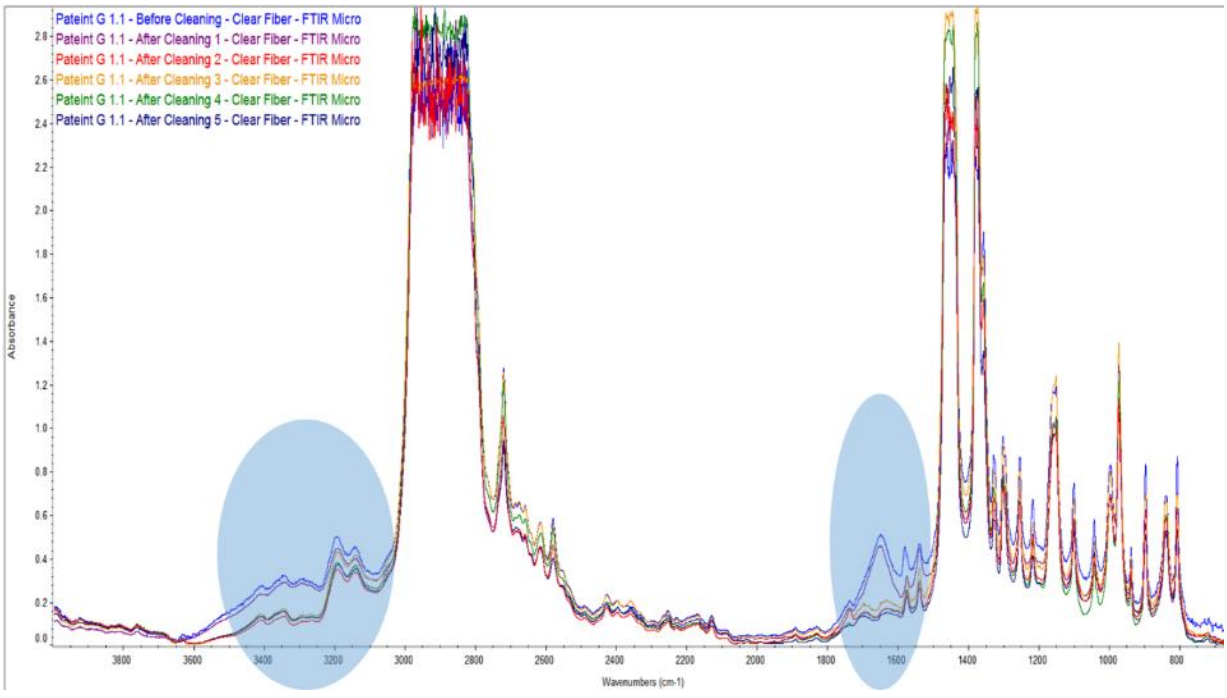


Figure 62. Patient G 1.1 Example FTIR demonstrating progressive protein removal from Blue Fiber after 5-cleaning cycles

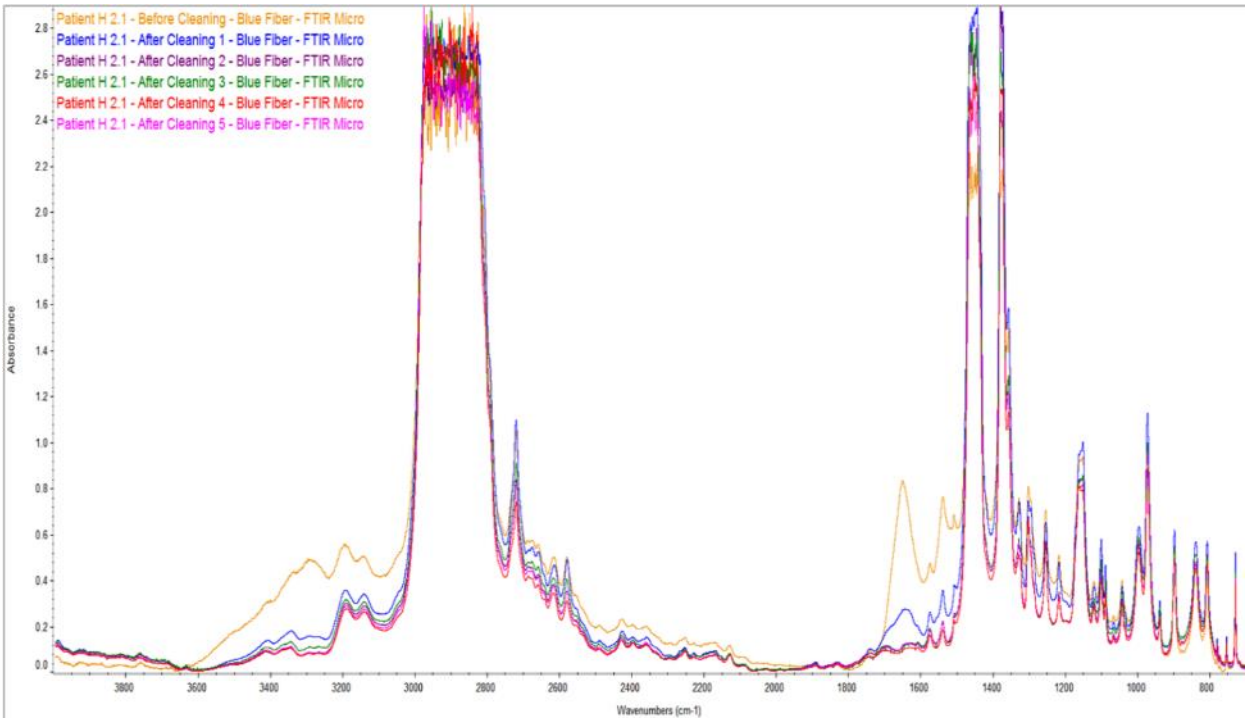


Figure 63. Patient H 2.1 Example FTIR demonstrating progressive protein removal from Blue Fiber after 5-cleaning cycles

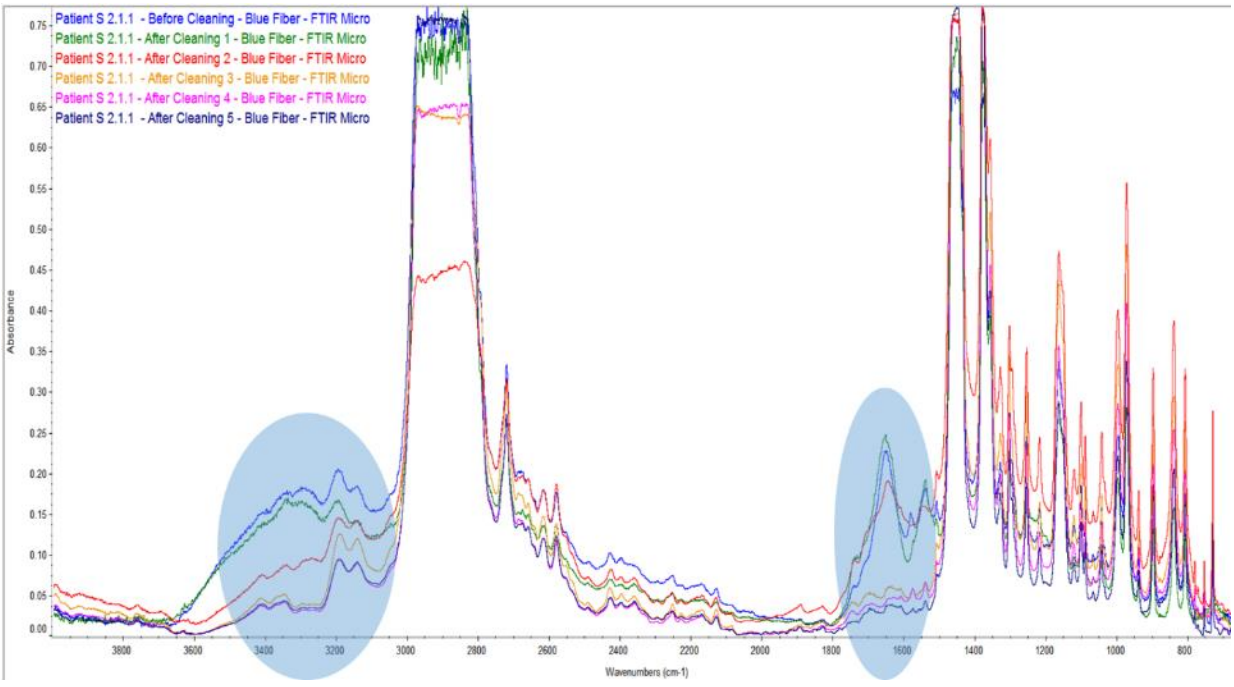


Figure 64. Patient S 2.1.1 Example FTIR demonstrating progressive protein removal from Blue Fiber after 5-cleaning cycles

The FTIR data proves, without question, surfaces of uncleaned explants are covered with adsorbed proteins. The examples given of the cleaning protocol and sequential protein removal

are the norm and not the exception. It is well known that collagen and other proteins chemically react with formalin during the fixation process and form a tightly adhered, hard, brittle, insoluble composite polymeric sheath around explant fibers. Consequently, in order to remove the crosslinked protein layer effectively, one must utilize knowledge of the protein-formaldehyde chemical reaction that creates the crosslinked product. The cleaning process was developed utilizing knowledge of the protein-formaldehyde crosslinking chemistry, and therefore is an effective cleaning process. This has been affirmed by FTIR analyses of cleaned Prolene explant fibers, LM, and SEM photo-microscopy on many occasions

Scanning Electron Microscopy (SEM) Images

SEM images at various cleaning stages depicts both the progression of explant fiber cleaning as well as the tenacity with which the formalin-protein coating adheres to Prolene. Figures 65 b. and 66 b. define the cracked surface appearance of the fibers and their origin. The easily observable ‘lock and key’ pattern of the formalin-protein coating (Patient 4 #1.1; SEM 12 or 2.1, SEM 10) perfectly describes cohesive failure of the formalin-protein coating (see Figure 65 a) and adhesive failure (see Figure 65 b) of this same formalin-protein composite layer from Prolene (this phenomenon is present for both samples, 1.1 and 2.1).

Furthermore, the cleaning process followed by SEM demonstrates visually that fiber surface degradation did not occur. The SEM images of Figures 65 and 66 show partial removal of the proteinaceous shell surrounding the fiber. The cleaned fibers in Figures 65 f. and 66 f. continue to possess extrusion lines created during fiber manufacture. If the surface of the Prolene fibers had degraded, as postulated by plaintiff’s expert, the extrusion lines would likewise degrade during this process and would no longer be visible – that is not the case we observed. Therefore, surface degradation of Patient 4 and other implants did not occur.

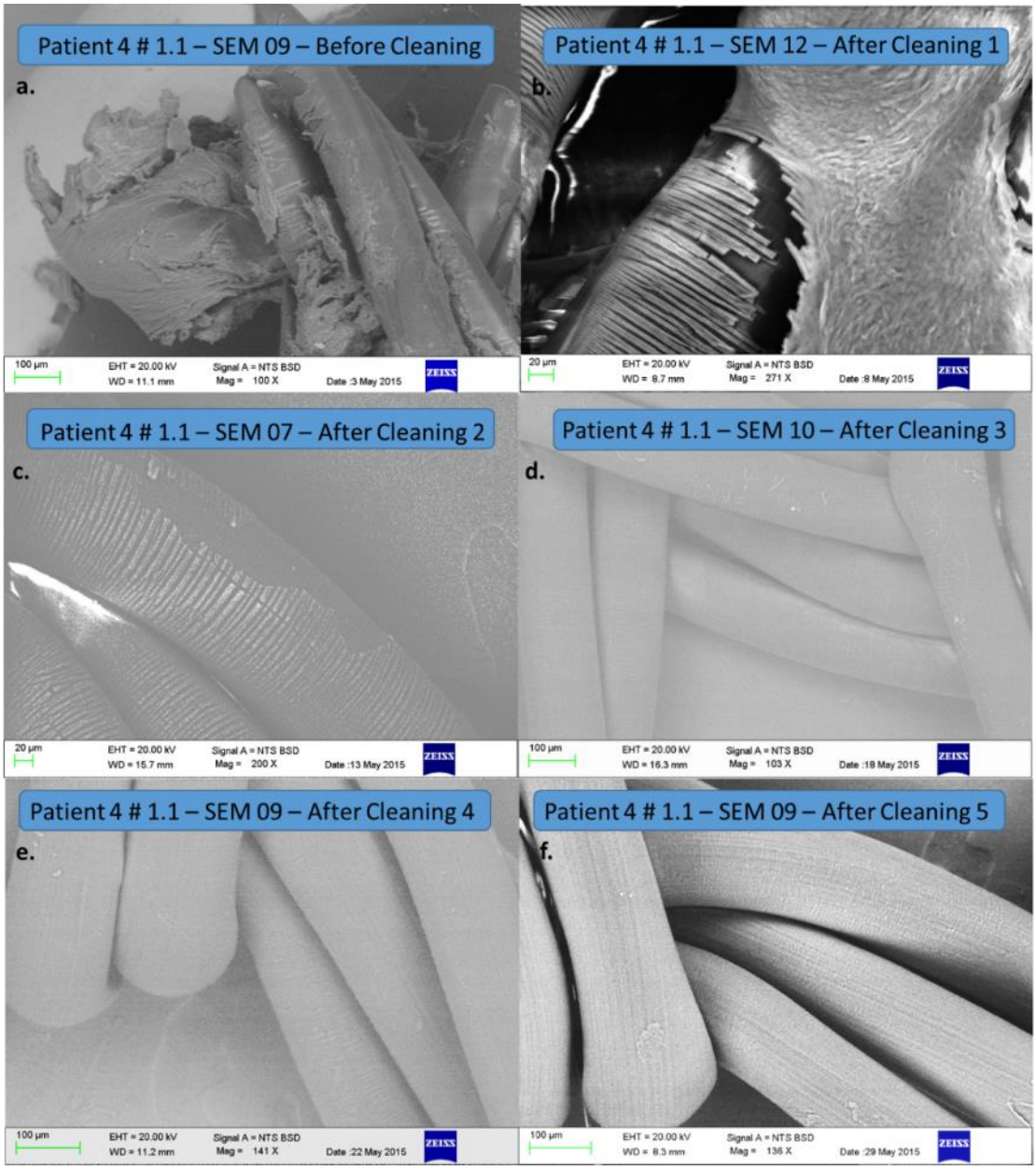


Figure 65. a., b., c., d., e., and f. – Patient 4 #1.1

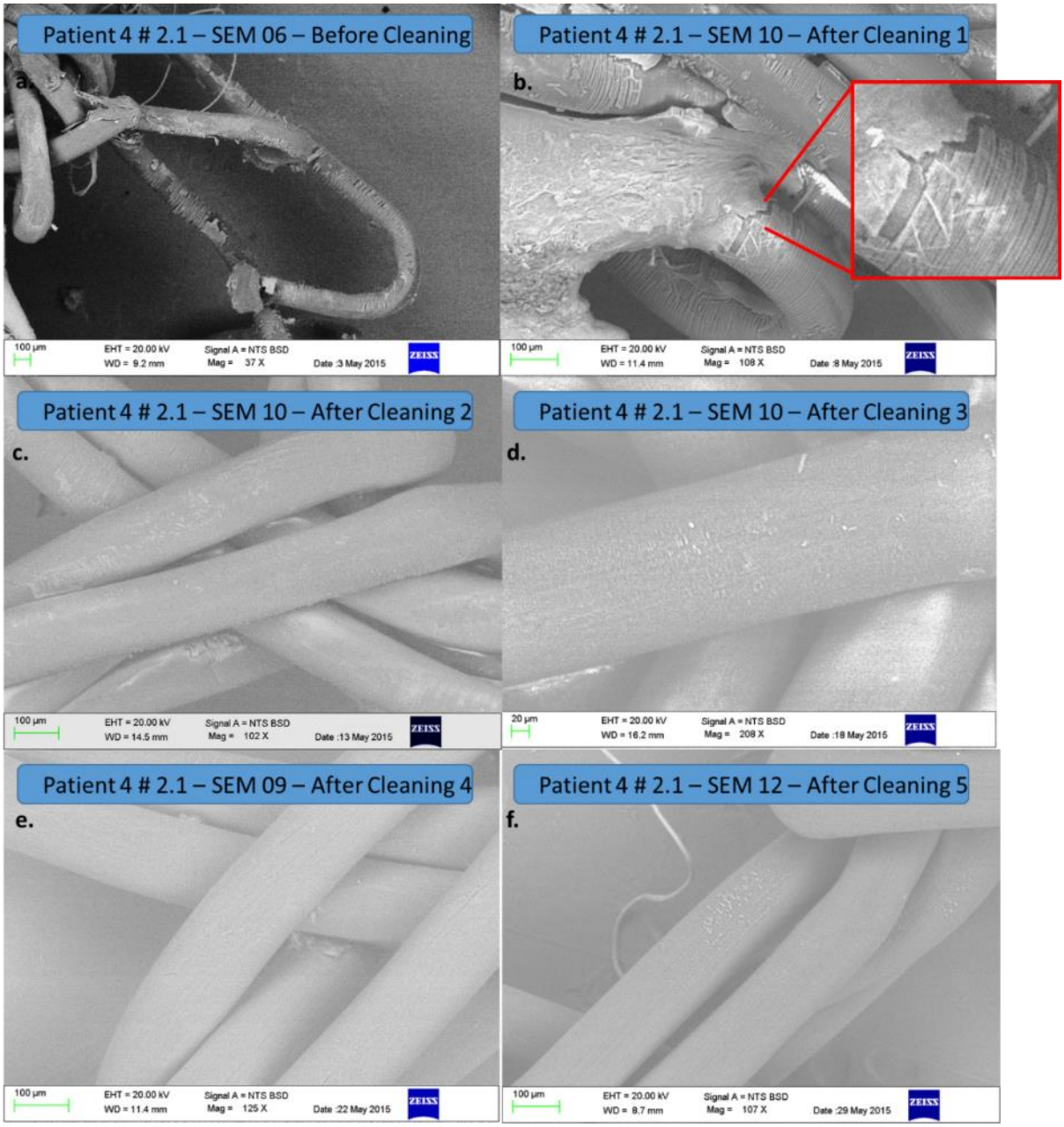


Figure 66. a., b., c., d., e., and f. – Patient 4 #2.1

Another excellent example showing protein attachement to the explant surface is shown in Figures 67 – 68 (Patient C explant). The light microscopy and corresponding FTIR microscopy conclusively demonstrates the composition of the clear/transluscent material on the blue explant surface is protein.

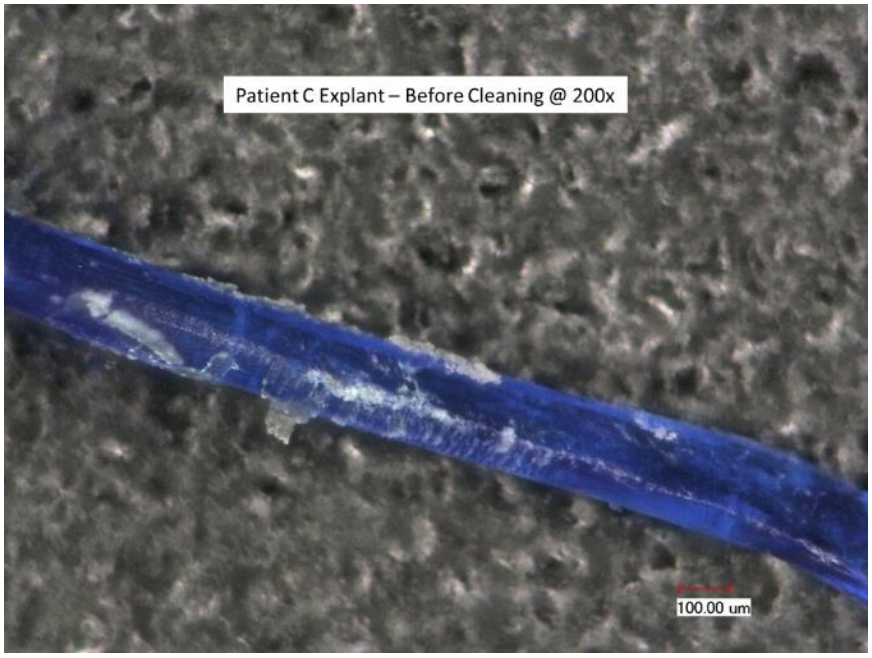


Figure 67. Patient C Explant – Before Cleaning @ 200x

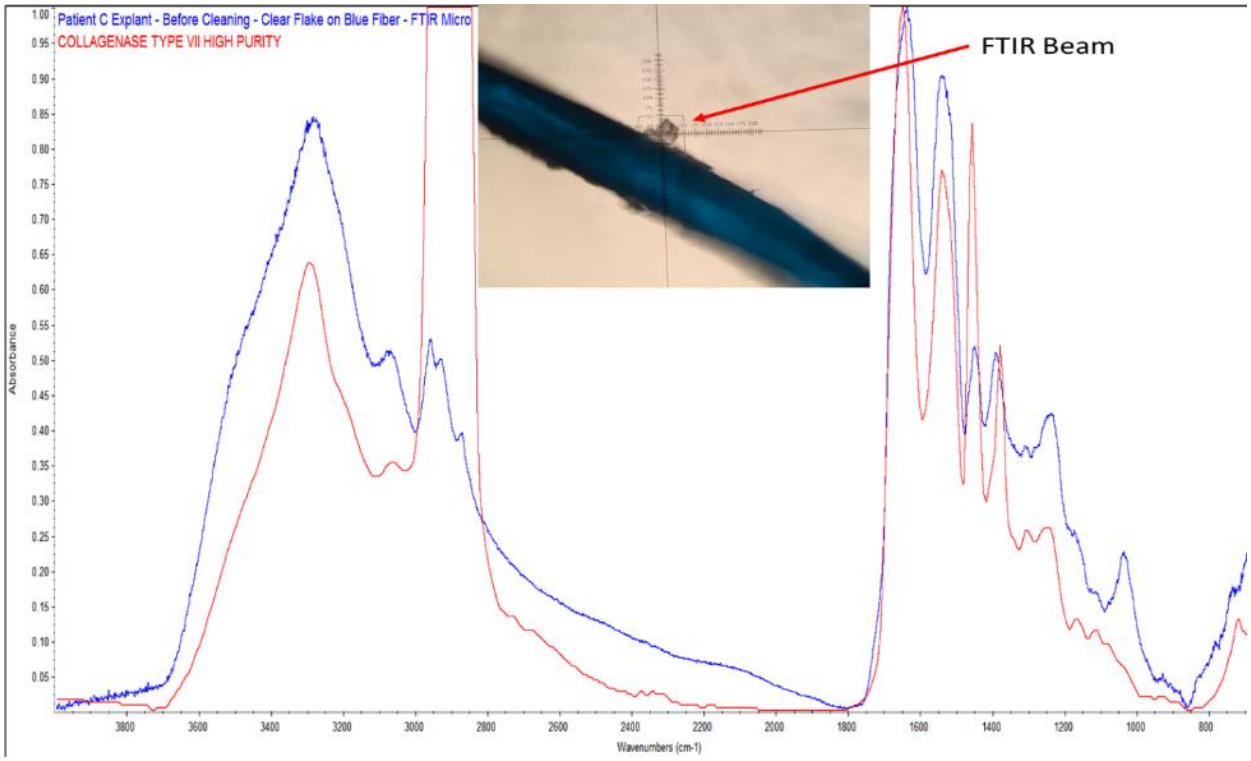


Figure 68. Patient C Explant – Before Cleaning @ 200x, FTIR Microscopy of Flake on Explant overlaid with Collagenase reference spectrum

Flawed Methodologies by Plaintiffs' Experts

- Plaintiff's pathologist has not identified or utilized a control of degraded polypropylene
- Plaintiff's pathologist opinions and statements are based on flawed methodology. They are in direct contradiction to well-established scientific principles of tissue staining given Prolene does not possess ionic charged groups or pH, both required for staining.
- Factors all explants have in common are, all are fixed in formaldehyde, all contain flesh, all form a formaldehyde-protein polymer or shell around mesh fiber(s), and all are subjected to histologic tissue processing. This sequence of events and polymer formation, is not recognized, or is ignored, by Plaintiff's pathologist.
- Plaintiff's pathologist has no way to know how degraded Prolene "looks" or "takes dye" any differently than pristine Prolene since he uses no experimental control
- Plaintiff's pathologist has no analytical data to confirm chemical composition of the "blue dots" and therefore his identification of two very dissimilar materials as "blue dots." This would require analysis by FTIR microscopy or other appropriate chemical analyses to distinguish chemical structures of the blue dots
- Guelcher's initial XPS data are flawed as his work shows only 4 of 17 samples possess C=O configurations while all samples contain this configuration due to additives employed in the manufacture of Prolene.
- Guelcher's data set for potential oxidation of Prolene continues through a six week period for TVT samples, while the polypropylene control experimentation covers only four weeks.
- Guelcher current work is flawed—add here

Summary of Opinions

- Prolene used in Ethicon's mesh products does not undergo meaningful or harmful degradation *in vivo*. My opinions are based on:
    - my personal extensive scientific investigation of the Patient 4 explant as well as numerous other explants (approximately 95) from similar cases involving Prolene, the same material used in Ethicon's product at issue,
    - the seven year dog study conducted by Ethicon beginning in November 1985 and reported October 15, 1992; and,
    - additional data and information reviewed and relied upon as referenced herein.
- Molecular weight degradation and carbonyl group formation are inextricably linked and you cannot have one without the other. Simply stated, if Prolene mesh is oxidized, its molecular weight will decrease and carbonyl bonds will form and the carbonyl bonds will

show themselves in the FTIR spectra. My laboratory data has shown explanted Prolene fibers do not exhibit carbonyl groups in the FTIR spectra and thus have not oxidized nor experienced significant molecular weight loss *in vivo*.

- Furthermore, for the explants I have examined, no evidence exists for meaningful molecular weight loss of Prolene. Thus, no meaningful Prolene degradation occurred while *in vivo*.

- It is my opinion, which is supported by experimental results, scientific data, and scientific literature, proponents of *in vivo* Prolene degradation have historically, erroneously, and consistently mis-identified adsorbed and strongly adhered proteins as Prolene and/or PP. Strongly adhered, crosslinked proteins are formed during the "formalin-fixation" process.

- Proponents of *in vivo* Prolene degradation have not considered well known and well established basic chemistry/polymer science principles and concepts. Consequently, these proponents have promulgated mis-information and mis-interpretation and in doing so have exacerbated confusion with respect to explant analyses; specifically they have not given consideration to the chemical reaction of formaldehyde with proteins which forms a hard, brittle, insoluble shell around Prolene and/or PP fibers. The hard shell encases mesh fibers. It is this hard, brittle, insoluble, protein-formaldehyde polymer surface coating that has been and continues to be mis-identified as degraded Prolene.

- I am unaware of any scientifically valid data supporting the tenet that Ethicon's Prolene meaningfully oxidizes or degrades *in vivo*, including the Patient 4 explant and other examples included herein that applies to any Prolene mesh product.

- The absence of meaningful, strong carbonyl absorption of Ethicon's Prolene FTIR spectra in my investigations conclusively proves the absence of scientifically significant Prolene degradation.

- The exceptional physical property data collected by Burkley, and included in his 7 year Dog Study Report, is profound proof that Prolene's physical properties did not degrade over a 7 year implantation period but, instead, improved. The basic principles of polymer science teach loss in molecular weight dramatically and adversely affects the physical properties of polymers. Additionally, it is well known that any oxidative loss of molecular weight of PP is accompanied by strong carbonyl bond (C=O) formation which readily appears in the FTIR spectrum. There is no evidence for C=O formation of PP during *in vivo* use, and no evidence of physical property losses. In fact, physical properties improved over time.

- I have not seen evidence suggesting rupture of Ethicon's Prolene fiber in the matter at hand, and it is my opinion that none will occur due to degradation, while used as *in vivo* implants of the type(s) investigated herein.

- There is no scientific evidence to support the contention that Ethicon's Prolene undergoes Environmental Stress Cracking *in vivo*. To the contrary, extensive evidence

exists, and has been reported herein, that polypropylene does not experience Environmental Stress Cracking (ESC).

- I have not seen FTIR data confirming oxidation or any type of degradation of the Patient 4 explant or any other patient explants I have examined. To the contrary, my data confirms the absence of Prolene oxidation.

- At this writing I have been unable to find valid and scientifically reliable data of any type to conclusively confirm the Patient 4 explant given herein as an example, or any others I have examined, experienced any degradation, oxidation, hydrolysis, ESC, or loss of any physical properties as a result of *in vivo* implantation.

- Additionally, our work has been submitted to a peer-reviewed journal based on findings discussed herein and entitled 'The myth: *in vivo* Degradation of Polypropylene-based Meshes'. It has been accepted and published in the scientific literature.[387] Oral presentations have also been given, one in Cape Town, South Africa and another in Denver, Colorado. The former was considered for and won the Best Basic Science Abstract Award at the IUGA 41st Annual Meeting, Awarded by the International Urogynecological Association, 2016.

- A small percentage of explants exhibit carbonyl peaks before cleaning and after cleaning cycle 1 which are attributable to tissue decomposition. The carbonyls are more frequently observed with explants received in the dry state (no formalin fixation or preservation). Forbes *et al.* noted these carbonyl-containing compounds as shown below in Figure 69.[388]

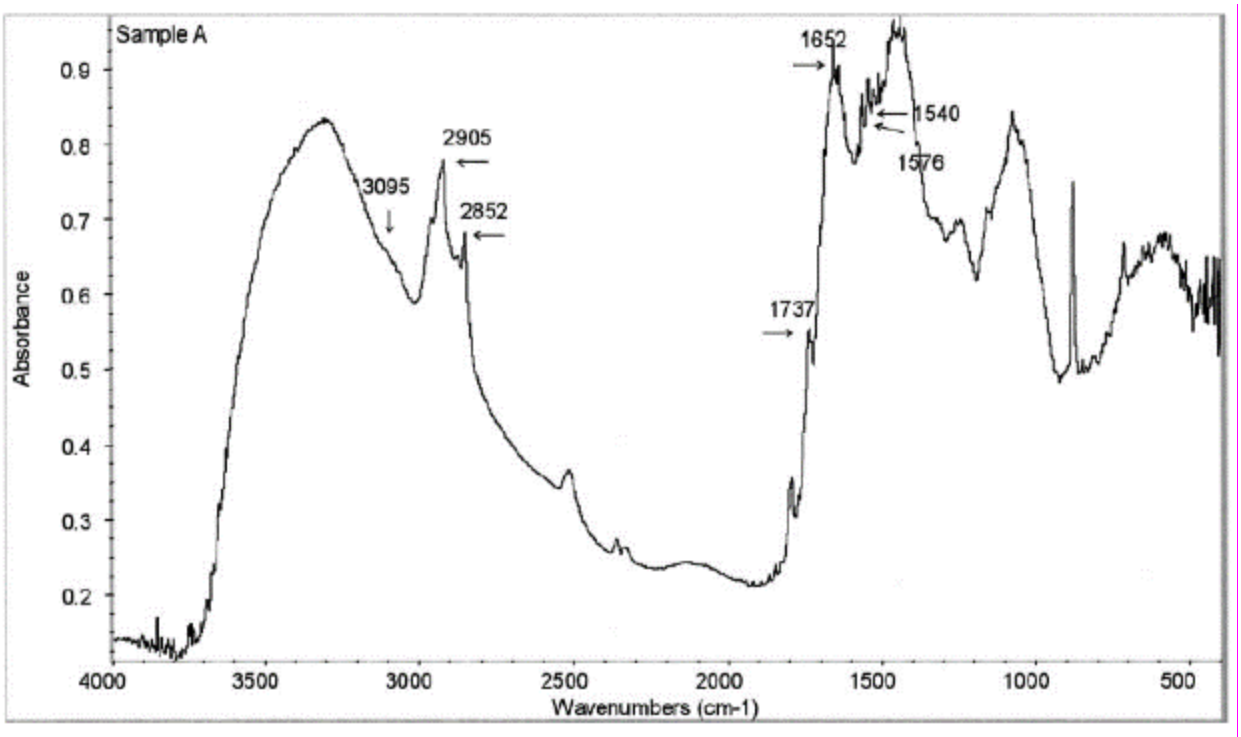


FIG. 5—*Infrared spectrum characteristic of early-stage adipocere formation (relevant peaks are assigned by arrows and wavenumbers).*

Figure 69 – Forbes *et al.* demonstration of carbonyl peak attributable to tissue decomposition[389]

I reserve the right to supplement this initial report and analysis, create additional exhibits as necessary to illustrate my testimony based upon the receipt of additional information, documents and materials, and to revise this report following the receipt of additional information and/or materials that have not yet been made available. As a supplement to my general report I rely on case specific reports served herewith.

Shelby F. Thames, Ph.D.
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